

RADIOLOGY

A MONTHLY JOURNAL DEVOTED TO CLINICAL RADIOLOGY AND ALLIED SCIENCES

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RADIOLOGY

A MONTHLY PUBLICATION DEVOTED TO CLINICAL RADIOLOGY AND ALLIED SCIENCES
PUBLISHED BY THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

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Short Esophagus with Esophagogastric or Marginal Ulceration¹

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New York, N. Y.

THE CHIEF PURPOSE of this report is to describe the roentgen and esophagoscopy findings in 29 cases of short esophagus with peptic ulceration at the esophagogastric junction. Short descriptions of the symptomatology and the treatment of these cases will be included. The condition to be described is identical with that called by Allison, Johnstone, and Royce "short esophagus with peptic ulceration" (2). Allison later included this combination of short esophagus and marginal ulceration under "reflux esophagitis" (4). It has also been described under such other names as "peptic ulcer of the esophagus" (3, 6, 8, 11, 16) and "peptic ulceration of the esophagus with partial thoracic stomach" (12, 20, 21).

It is difficult to choose a satisfactory designation for this entity, since there must remain at the present time considerable reservation as to its pathogenesis. The difficulty lies in the uncertainty as to whether the short esophagus demonstrable at the time of the examination is congenital or acquired. An additional confusing factor is the circumstance that, even though the final state may be in largest part acquired, congenital predisposing factors may be necessary. We shall describe the findings in our cases without making as-

sumptions as to their pathogenesis. It must therefore be emphasized that the term "short esophagus" as used in this paper indicates that the esophagogastric junction is located above the esophageal hiatus of the diaphragm and that the esophagus is not redundant. The esophagus is seen to be short both on roentgen and on esophagoscopy examination, although neither of these diagnostic methods permits differentiation of congenital from acquired shortening. In a similar fashion, for convenience of description, the gastric pouch above the diaphragm, which must be present in every case of short esophagus, may be designated as a "hiatus hernia." The use of the latter term to include both acquired and congenital pouches has a precedent, since in Åkerlund's basic contribution on hiatus hernias both congenital and acquired types were described (1).

There have been three constant features in our series of cases: (a) The esophagus was short, *i.e.*, the junction of the esophagus and the stomach, as determined by the nature of the lining epithelium, was above the esophageal hiatus of the diaphragm. (b) Free reflux or regurgitation of gastric contents into the gastric pouch above the diaphragm and from the pouch into the esophagus has been present. (c) Ulcera-

¹ From the Department of Roentgenology (Chief, Dr. Bernard S. Wolf) and the Department of Otolaryngology (Chief, Dr. Rudolph Kramer), The Mount Sinai Hospital, New York. Presented in part at the Thirty-eighth Annual Meeting of the Radiological Society of North America, Cincinnati, Ohio, Dec. 7-12, 1952.



Fig. 1. Gross specimen of a large esophagogastric or marginal peptic ulceration. A moderately severe esophagitis around the ulcer and for several centimeters proximal to it is also present. Stenosis is minimal.

tion at the esophagogastric junction has been demonstrated.

Before proceeding to a description of the roentgen and esophagoscopy findings, it is appropriate to state the criteria which were used to establish the presence of the features noted above. It is well known that the x-ray criteria for the identification of the esophagogastric junction are frequently equivocal. However, in the cases of this series, because of the presence of inflammatory changes or stenosis, there was no difficulty in recognizing the fact that this junction was above the hiatus in the diaphragm. Moreover, the gastric pouches in these cases were of sufficient size—3 cm. or more in diameter—that a typical configuration and a gastric mucosal pattern were usually demonstrable. Occasionally, in a case of severe stenosis of the esophagogastric junction, re-examination after dilatation was required before sufficient barium would pass the site of

narrowing to outline the gastric pouch adequately. The distance from the incisor teeth to the esophagogastric junction was carefully measured along the rigid esophagoscope. This distance ranged from 25 to 37 cm. as compared with the normal distance of 38 to 40 cm.

Regurgitation of gastric contents into the esophagus was demonstrated on roentgen examination by procedures to be outlined below. Little diagnostic significance was attributed to regurgitation of only small amounts of barium, particularly if this occurred after a considerable interval or as a result of maneuvers which significantly increased intra-abdominal pressure. In the presence of marked stenosis, insufficient barium may enter the stomach to permit the demonstration of regurgitation by roentgen methods. However, at esophagoscopy, free retrograde flow of gastric juice into the esophagus was noted in every case, before the tube entered the hernia sac, despite the fact that occasionally the esophagogastric junction was no more than 2 mm. in diameter. When tested with litmus paper, the regurgitated juice always gave an acid reaction.

The diagnosis of peptic ulceration was made by the observation esophagoscopically of a discrete ulcerated area, biopsy of which was reported by the pathologist as showing the "changes characteristic of a chronic peptic ulcer as seen in the stomach or duodenum." The term "ulceration" is used rather than "ulcer," since the ulcerated area is superficial and rarely has a punched-out ulcer appearance with elevated or indurated edges. In each case of the present series, the ulceration was "marginal" (Fig. 1), that is, it was surrounded by esophageal mucosa except at its distal border, where gastric mucosa was always visualized. Biopsy confirmed these observations. According to Allison *et al.*, the ulceration is not necessarily marginal but may be within 1 cm. of the esophagogastric junction. The fact that in several instances biopsies showed gastric mucosa bordering the ulcer in a single section contradicts the suggestion of Allison and

his associates that a prolapsing cuff of gastric mucosa is mistaken by the esophagoscopist as the distal margin of the ulcer. In several cases, biopsies were taken at multiple levels below the ulceration, and all showed exclusively gastric mucosa. These findings ruled out the possibility that the gastric epithelium seen at the distal edge of the ulceration was "ectopic." On the contrary, the pouch below the ulceration was lined by continuous gastric mucosa (Fig. 1).

In many instances, the mucosa of the esophagus for a variable distance proximal to the ulceration appeared reddened and edematous, sometimes with areas of leukoplakia—that is, an esophagitis was associated with the marginal ulcer. Marked narrowing of the esophagus itself, as seen in severe esophagitis, was not observed. However, while the degree and extent of the associated esophagitis were quite variable, the finding of the discrete marginal ulcerated area was constant.

ROENTGEN EXAMINATION OF THE ESOPHAGUS

In order to demonstrate all of the diagnostic features of this condition, the roentgen examination of the esophagus must be carried out with the possibility of ulceration in mind. Since the absence of a normal mucosal pattern and the presence of a constant flat ulcer patch are the important signs of inflammatory change and ulceration, multiple views of the esophagus and gastric pouch with varying amounts of barium are indispensable. The difficulty of the examination is increased in cases without stenosis, since the flow of the barium mixture from the esophagus into the stomach in such instances is usually more rapid and more continuous than is ordinarily seen. The passage of the usual thin barium mixture should be observed and recorded radiographically in the erect and recumbent positions, preferably in both right and left oblique projections. The recumbent oblique projections are usually taken with the patient prone, although in a troublesome case supine oblique projec-

tions may also be helpful. "Spot" radiography is a necessity if the phases of maximum distention of the esophagus and the gastric pouch are to be recorded.

In order to obtain "a double-contrast" examination of the esophagus, an attempt may be made to have the patient swallow air as well as barium. Various maneuvers such as continuing to drink after the glass is empty, or sucking air through a straw, or the use of a carbonated beverage after a pasty barium mixture, may be tried. Double-contrast views thus obtained are particularly useful because maximum distention appears to occur more consistently with air or gas than with barium. Pasty or thick barium mixtures may be useful in demonstrating ulcer patches. Thick mixtures, however, should be postponed until the end of the examination to avoid irregular retention of small amounts of barium in the lower end of the esophagus.

The level of the esophageal hiatus has been identified by noting the site of the pinchcock action of the diaphragm on deep inspiration while barium is being swallowed (14). Even in the presence of a large hernia, this pinchcock action is easily observed, although atypical. The phase in which respiration is suspended determines to a considerable degree the appearance of the barium column at the level of the hiatus. To avoid variations in appearance due to respiration, it is preferable to take radiographs during continuous swallowing of the barium mixture. Since respiration is physiologically suspended during this act, satisfactory roentgenograms can be obtained if the patient is sufficiently co-operative to drink continuously.

In order to demonstrate reflux of gastric contents roentgenologically, the stomach must be filled with the usual thin barium mixture and the examination performed before sedimentation of the barium. After the esophagus and the hernial sac have been checked in the erect position, to make sure that they are empty, the patient is placed on the fluoroscopic table in such a position that the barium distends the stom-



Fig. 2. Reflux of barium from stomach into hernial sac and into the esophagus when the erect patient bends over—the "Johnstone" position.

ach in the region of the hiatus. The optimum position is usually secured by first placing the patient on his back and then elevating the left side as much as necessary. Retching may be differentiated from regurgitation by the presence of nausea and by its episodic nature. Various maneuvers may be utilized to encourage or increase regurgitation. With the patient on his right side or prone, the table may be tilted so that he assumes the Trendelenburg position. Manual compression of the abdomen, the Valsalva maneuver, a swallow of water, or flexing the head and thighs will also accentuate regurgitation. If the patient is not too weak, the "Johnstone position" (Fig. 2) may be utilized to demonstrate reflux. This position is useful since it does not require the recumbent posture. The erect patient bends over as if to touch his toes with his fingers, and the region above the diaphragm is observed or radiographed in the lateral projection. The forearms must be kept behind the head to remove the scapulae from the field.

ESOPHAGOSCOPIC FINDINGS

Gastric juice is encountered as soon as the esophagoscope enters the upper esophagus, requiring continuous aspiration as the tube is passed. In a typical case, at about 34 or 35 cm. from the incisor teeth,

a discrete somewhat serpiginous or oval ulcerated area, 1 to 3 cm. in length, covered by a whitish diphtheritic membrane, is seen (Fig. 3). The ulceration may or may not extend around the entire circumference of the esophagus. The membrane is in most cases easily removed

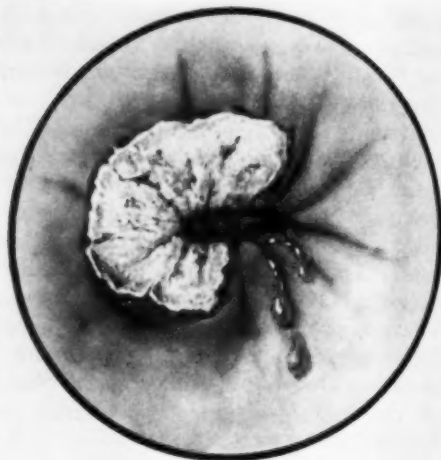


Fig. 3. Drawing of esophagogastric ulceration as seen through the esophagoscope. Ulceration is superficial and covered with a diphtheritic membrane. The distal margin of ulceration is at the esophagogastric junction, which is narrow but constantly patent, permitting free regurgitation.

with the forceps, leaving a slightly bleeding, red, granular surface. The margins of the ulcer show only slight elevation. At the level of the ulceration, the lumen of the esophagus is moderately narrowed but still easily distensible. The esophagogastric junction is observed at the distal margin of the ulceration. The characteristic feature of the lumen at this point is its unvarying appearance and constant patency. When stenosis is present, it is maximum at the esophagogastric junction. The degree of narrowing and amount of rigidity within the stenotic segment are quite variable. Occasionally, the stenosis is easily overcome by simple pressure on the esophagoscope. In other cases, however, repeated dilatation with Jackson wax bougies of increasing diameter is required. In contrast to the marked rigidity in the presence of carcinoma, dilatation can

usually be achieved at a single sitting from a diameter of 20 French up to 36 French. A localized mass or protrusion into the esophageal lumen, as seen with tumors, is not observed. Nevertheless, a biopsy of the ulcerated area is routinely taken to confirm the diagnosis.

Although in every case a marginal ulcer was noted on esophagoscopy, a discrete ulcer crater was seen only rarely on roentgen examination. This must be attributed to the superficial nature of the ulceration. Despite the absence of a crater, however, as noted below, the segment in which the ulceration was present could be identified roentgenologically. For convenience of description, we refer to the portion of the esophagus for about 2 to 3 cm. immediately proximal to the esophagogastric junction as the "marginal" or "junctional" segment.

ROENTGEN FINDINGS

The most significant findings on roentgen examination were:

(1) A short esophagus entering at the apex or summit of a gastric pouch. The esophagus, the gastric pouch, and the fundus of the stomach joined each other without any abrupt or acute angulation.

(2) Effacement of the mucosal pattern and changes in distensibility in a short segment at the junction of the esophagus and the gastric pouch. The esophagogastric junction corresponds to the lower border of this marginal or junctional segment. Since an ulcer crater within this segment was demonstrated in only 6 of the 29 cases (Fig. 4), the roentgen diagnosis of marginal ulceration must be based on these more indirect findings.

(3) Free reflux of barium from the stomach into the esophagus if stenosis was not marked.

Review of the films suggested that the group as a whole could be divided into two varieties with differing roentgen features. The first type was characterized by the presence of definite stenosis and obstruction in the marginal segment, while the second variety showed no absolute

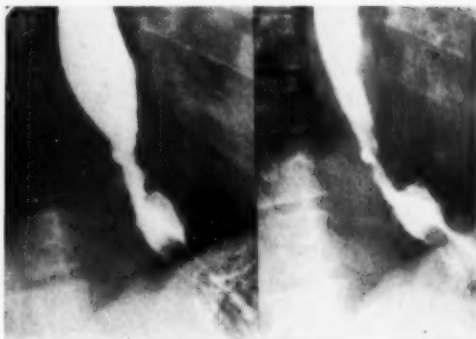


Fig. 4. Short esophagus with marginal ulcer. Unusual example in which the ulcer crater within the marginal segment was demonstrable. The esophagus is straight; its lower portion is fusiform.

narrowing and no delay to the passage of the barium mixture.

Stenotic Type: In the stenotic group, a marginal segment of marked narrowing, rarely longer than 1 cm. and frequently only several millimeters in length, was demonstrated, usually from 3 to 8 cm. above the hiatus in the diaphragm (Figs. 5B, 6A, 6B, 7). In one case, this segment was located just below the arch of the aorta (Fig. 8). There was a total absence of mucosal pattern within the narrowed area, which frequently appeared as a frayed thread, *i.e.*, ulceration was present. The presence of constant narrowing of unvarying appearance was often not immediately evident, because of the difficulty of obtaining films showing complete filling of the esophagus above and of the gastric pouch below.

With incomplete filling, particularly of the apex of the hernial sac, a longer segment, irregular in course and in caliber and difficult to interpret, was a common observation. With complete filling, the esophagus proximal to the marginal segment was usually somewhat fusiform or conical, with somewhat bulging, rounded sides. Occasionally, it was almost triangular, with only slightly bulging contours. This conical segment may be quite short and continuous above with a moderately narrowed cylindrical segment several centimeters long, which gradually widens into a normal but slightly dilated

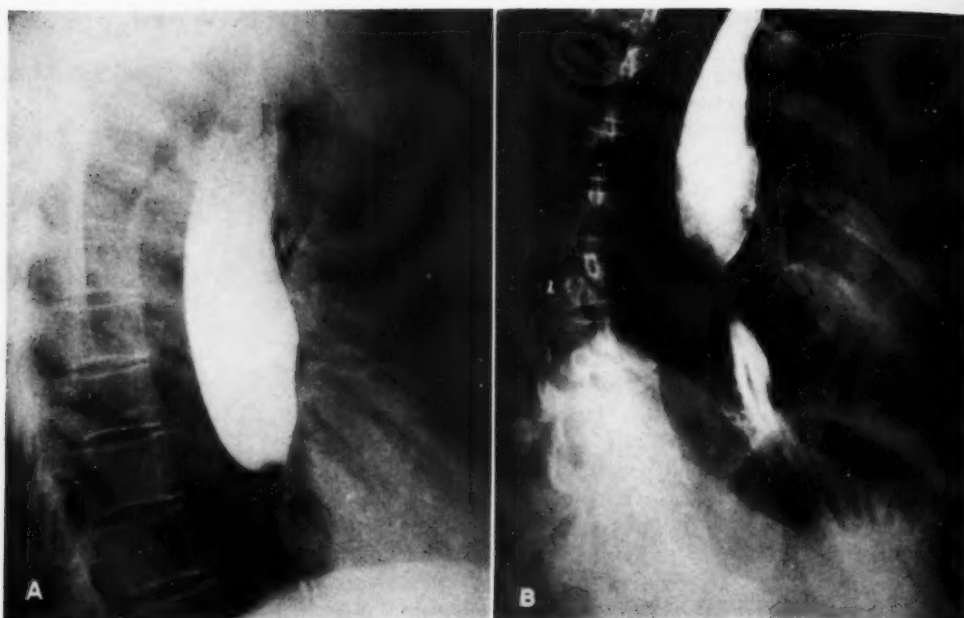


Fig. 5. A. Marginal ulcer 6 cm. above the diaphragm with marked stenosis. A filling defect is present, due to retained food. Insufficient barium passes the stenotic esophagogastric junction to distend the gastric pouch, which may be mistaken for esophagus.

B. Same case after dilatation, with clear demonstration of the gastric pouch. Markedly narrowed junctional segment 4 mm. in length. The apparent greater length of this segment is due to the narrow triangular apex of the hernial sac, which is difficult to distend completely. Total absence of mucosal pattern within the junctional segment is indicative of marginal ulceration.

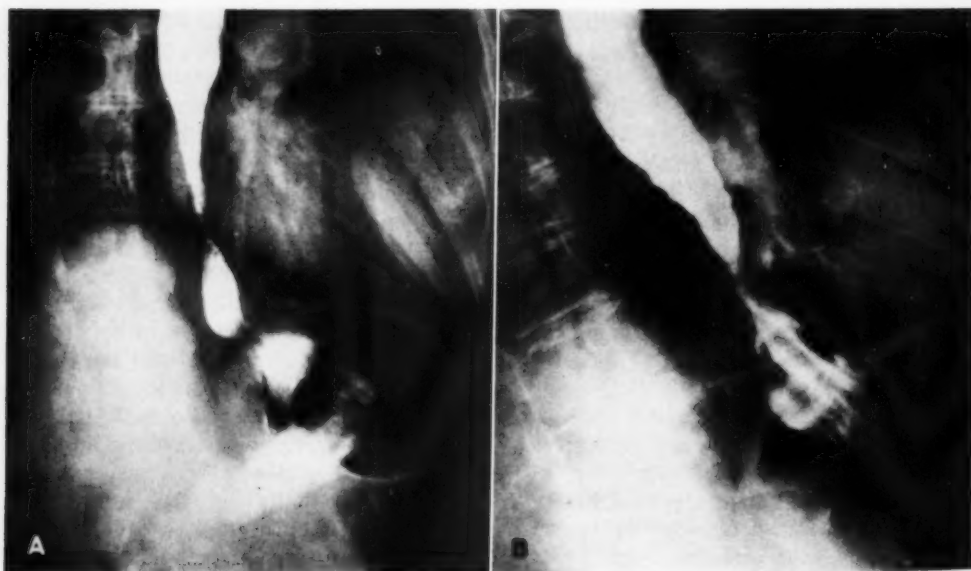


Fig. 6. A. Short esophagus with marginal ulcer, stenotic type. Stenotic junctional segment with absence of mucosal pattern 1 cm. in length, 5 cm. above the hiatus. The esophagus proximal to the junctional segment is narrowed in fusiform fashion, with fine irregularities along its contour, indicative of an associated esophagitis.

B. Same case after dilatation and medical therapy. The lower end of the esophagus is now more distensible. Irregular tertiary esophageal contractions.

esophagus. Above the marginal segment, the esophagus, even when narrowed, appeared to be pliable, with contours changing with the degree of filling. Despite the presence of marked stenosis, the esophagus proximally was only moderately dilated. Its motor function occasionally appeared to

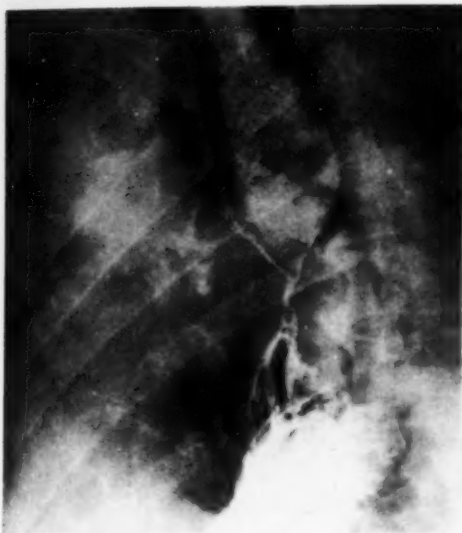


Fig. 7. Short esophagus with marginal ulcer, stenotic type. Left anterior oblique projection. Markedly narrowed segment 5 mm. in length with absence of mucosal pattern. Triangular esophagus above and triangular gastric pouch below produce a spindle or bow-tie appearance. With greater filling, the contours of the lower end of the esophagus bulged laterally, indicating absence of rigidity.

be disturbed, with prominent tertiary contractions. The mucosal pattern above the marginal segment was frequently quite indistinct, indicating an associated esophagitis. With an indistinct mucosal pattern, the borders of the esophagus showed minute spiculation. Immediately below the marginal segment, if sufficient barium traversed the stenosis, a gastric pouch was demonstrable, usually with quite distinct folds radiating toward its apex. No portion of the pouch was above the esophagogastric junction. The triangular configuration of at least the upper portion of this pouch was characteristic and rather striking in contrast to the convex bulging sides of the usual pulsion type of hiatus hernia. There was no evi-



Fig. 8. Marginal esophagogastric ulceration located just below the level of the aortic arch. Biopsy of tubular structure below ulceration showed gastric epithelium.

dence of any filling defect within the hernial sac nor of any destruction of the gastric mucosal pattern. The general appearance of the short marginal segment of marked narrowing, the tapering esophagus above, and the triangular gastric pouch below suggested in several cases the appearance of a spindle or bow-tie (Fig. 7).

With the patient erect, the gastric pouch may become elongated and the mucosal folds within it may appear thinner and more longitudinal. However, it was always demonstrable in the erect position, although it occasionally appeared somewhat smaller than when the patient was recumbent. The fact that a gastric pouch or hiatus hernia was present could not be unequivocally demonstrated if only a small trickle of barium passed the stenotic segment. This trickle of barium may create the appearance of a longitudinal tubular structure which would ordinarily be called esophagus (Fig. 5A).

Non-Stenotic Type: The smaller, non-stenotic group, 7 of the 29 cases, was clearly identified only after the roentgen picture in the stenotic cases was clarified.

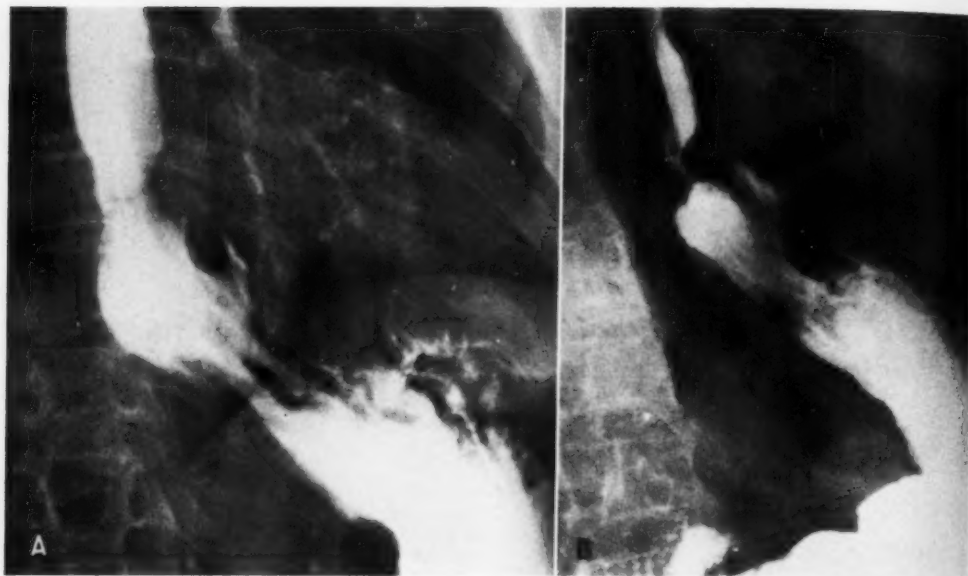


Fig. 9. A. Short esophagus with marginal ulceration, non-stenotic type. Patulous, incompletely distensible junctional segment 2 cm. in length with straight, parallel borders and markedly distorted mucosal pattern. The esophagus is straight and enters the summit of the hernial sac, which is globular in shape.

B. Same case with less barium. Effaced mucosal pattern in junctional segment; small nodular defect (localized epithelial thickening); widened folds in gastric pouch.



Despite the absence of stenosis, it was possible to suspect the presence of esophagogastric ulceration because of the lack of distensibility in the marginal segment and its disturbed mucosal pattern. The findings on esophagoscopy were identical with those in the group with stenosis except for the absence of narrowing at the esophagogastric junction. A relative stenosis, however, in the sense that complete distensibility was not present, was sufficient to cause dysphagia. The marginal segment, 1 to 2 cm. in length, appeared band-like, with straight parallel borders (Fig. 9A) or a distinctly angular contour on one or the other wall (Fig. 10A and B). Within this segment the normal mucosal pattern was obliterated (Fig. 9B), and in 3 cases a constant, oval smudgy patch of barium was seen, highly suggestive of a

Fig. 10A. Short esophagus with marginal ulcer, non-stenotic type. Patulous junctional segment which shows lack of distensibility, indistinct mucosal pattern, and a constant notch or angular contour which may represent the ulcer crater.

flat ulcer patch (Fig. 11A and B). These cases occurred in older patients with a globular or pulsion type of hiatus hernia but in whom the junction of the esophagus with the herniated pouch was unusually wide and straight. Moreover, this junction appeared to be constantly patulous.



Fig. 10B. Same case as Fig. 10A, erect position. Without the notch as a landmark, the gastric pouch might be missed.

The esophagus was only moderately dilated and not redundant and entered the hernia at its summit in symmetrical, concentric fashion. No portion of the hernia was above the esophagogastric junction. Above the marginal segment the esophagus appeared to be unusually distensible, with poorly marked peristalsis. Aerophagia was pronounced. The folds of the gastric pouch occasionally appeared somewhat thickened and irregular in course, but no evidence of ulceration within the sac could be demonstrated. The gastric pouch persisted when the patient was erect, although its identification was considerably more difficult.

This group of cases showed the most marked and prompt regurgitation of gastric contents into the esophagus. While the patient swallowed barium continuously, the neck of the gastric pouch within the



Fig. 11. A. Short esophagus with marginal ulcer, non-stenotic type. Patulous but relatively non-distensible junctional segment 6 cm. above hiatus. An ulcer patch 1.5 cm. in diameter is faintly seen through the barium column, in the junctional segment. Gastric pouch shows bulging sides.

B. Ulcer patch seen better with less barium.

hiatus narrowed to a considerable degree on deep inspiration. Narrowing on deep inspiration did not occur to the same extent during regurgitation. In fact, regurgitation was greatest on deep inspiration. This indicates that the diaphragm-



Fig. 12. "Pulsion" hiatus hernia with secondary or acquired shortening of the esophagus. Patulous esophagogastric junction and marked regurgitation but no evidence of marginal ulcer or esophagitis.

matic pinchcock action in these patients is for some unknown reason much less effective during regurgitation than during swallowing and suggests a motor dysfunction in the sense of a dissociation between the action of the crural fibers of the diaphragm and the domes of the diaphragm. This apparent independent action of the crura and the remainder of the diaphragm seems more reasonable when it is recalled that several authors believe that the motor innervation of these portions is different (10). Incidentally, the roentgen appearance of the hernia and the esophagus filled from below by regurgitation is rather characteristic. The filling is in the form of a continuous column without any evidence of motor action until the barium is propelled downward again by the peristaltic action of the esophagus beginning near the level of the aortic arch.

It should be emphasized that the diagnosis of marginal ulceration without stenosis is extremely difficult on the basis of the

roentgen findings alone unless a constant patch of barium is seen or an unequivocal abnormal marginal segment is demonstrated. There are individuals (Fig. 12) who show a short esophagus, an hiatus hernia, a patulous esophagogastric junction, and a wide hiatus with marked regurgitation who do not have esophagogastric ulceration. In these patients marginal ulceration may presumably develop if gastric acidity is high (4).

CORRELATION OF ESOPHAGOSCOPIC AND ROENTGEN FINDINGS

There has not been an exact correlation between the degree of rigidity or narrowing of the esophagogastric junction found on esophagoscopy with the findings on roentgen examination. In two cases, in which a rather wide though non-distensible esophagogastric junction was demonstrated roentgenologically, a fairly marked narrowing was noted on esophagoscopy. The narrowing in these cases, however, was easily overcome by the esophagoscope and presumably was, at least in part, spastic in nature. The level of the esophagogastric junction as determined roentgenologically has in general been confirmed by esophagoscopy. Whenever there have been definite narrowing and lack of distensibility of the esophagus above the marginal segment on roentgen examination, a distinct esophagitis as well as a marginal ulcer has been noted at esophagoscopy.

PATHOGENESIS

The pathogenesis of "short esophagus" with esophagogastric or marginal peptic ulceration has been discussed in detail in the literature. There appears to be no doubt that regurgitation of acid gastric contents into the esophagus is the immediate cause of the ulceration. Whether ulceration will occur in any particular individual will depend on the amount and concentration of acid in the gastric juice, particularly in the fasting or night gastric contents, the duration of contact, the extent of neutralization by swallowed saliva, and other unknown factors.

Regurgitation is possible only if the retrograde course of the gastric contents, under the influence of the difference in pressure between the abdomen and the mediastinum, meets no anatomical or valvular block—that is, this pathway must be unobstructed and without abrupt

esophagogastric junction is normally variable and may give way under the pressure of regurgitated contents or may perhaps actively relax in some cases. Failure of the intrinsic and extrinsic sphincters, when superimposed on the suitable anatomical features, results in regurgitation.

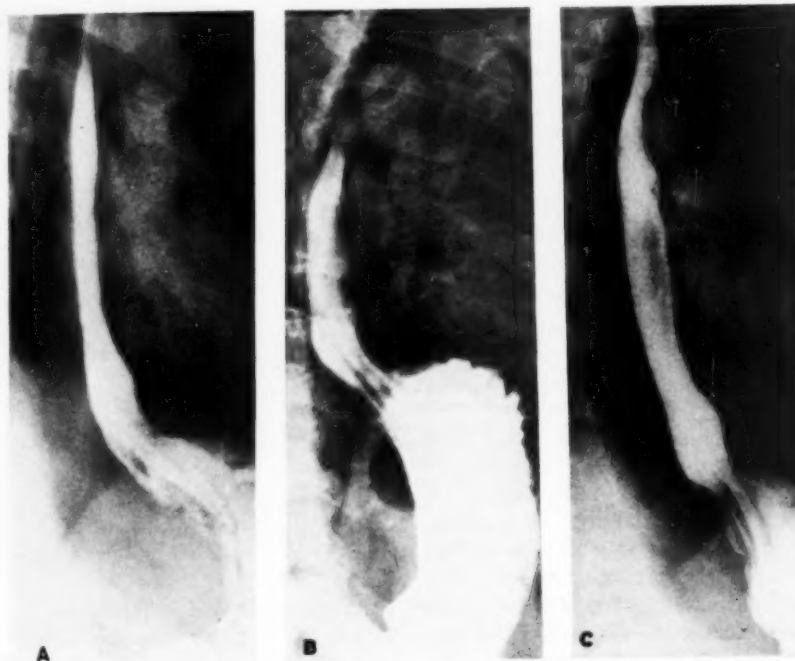


Fig. 13. Three different individuals with a "family" resemblance. Gastric folds extend through a wide hiatus and join the fundus of the stomach without any acute angulation; no evidence of intrinsic sphincter action. Short esophagus due to "fixation-failure"?

angulation. A hiatus hernia, with the exception of the paraesophageal form, obliterates the normal acute infradiaphragmatic esophagogastric angle. In the absence of a hiatal hernia, regurgitation and marginal ulceration are most unusual. The sphincters along this pathway must also become ineffective in preventing regurgitation. As pointed out above, in association with widening of the hiatus and herniation, there may be failure of the crura to contract sufficiently to prevent regurgitation even though, during swallowing, a rather effective pinchcock action at the hiatus can be noted. The effectiveness of the intrinsic sphincter action at the

The suitable anatomical features—that is, a straight, short esophagus entering directly into a gastric pouch above the diaphragm, associated with a wide hiatus and the absence of any acute angulation from the esophagus to the stomach—may be recognized roentgenologically before ulceration occurs. The assumption that these factors are precursors of marginal ulceration is strengthened by the fact that they may be noted with and without free regurgitation in different patients. The most common type of hernia which fulfills these requirements is the well known pulsion or "sliding" hiatus hernia, which is generally accepted

as acquired (5, 17, 19, 22). It is attributed to increase in the pressure differential between the abdomen and the mediastinum and a weakening of the fascial attachments of the esophagogastric junction to the diaphragm incident to advancing age. The hernial sac is characteristically globu-

assumed, however, without further evidence, that other types of short esophagus, presumably developmental in nature, may not also be precursors of marginal ulcer (6, 20). In this connection, attention may be called to a rather frequent roentgen appearance in the region of the hiatus



Fig. 14. A. "Fixation-failure" short esophagus. On deep inspiration, effective pinchcock action at hiatus. Dilatation of lower end of esophagus (phrenic ampulla) and small hernial sac with no evidence of intrinsic sphincter action between these structures. B. Same case. Gastric folds extend above the hiatus, which appears wider than is ordinarily seen while barium passes through. C. Same case after barium bolus has passed. Gastric mucosal folds appear to retain barium in contrast to the esophageal mucosa above.

lar in shape, with bulging sides indicative of relatively high pressure within it. It must be emphasized that in many, if not most, cases of pulsion hernia, the esophagus becomes shortened *pari passu* with the development of the hernia (22). The slack, which would otherwise be produced by a portion of the stomach entering the chest, is taken up because of the normal physiological tendency of the esophagus to be as short as its attachments above and below will permit (7). This type of short esophagus is therefore acquired. Pulsion hernias may be reduced spontaneously in the erect position. However, failure to demonstrate the hernial sac may be technical in nature, due to inability to distend it with the patient in this position.

The transition from a pulsion hernia with patulous esophagogastric junction and secondary or acquired shortening of the esophagus to the non-stenotic variety of marginal ulcer is plausible, since the roentgen features, except for the presence of ulceration, are identical. It cannot be

which has been noted both with and without regurgitation. Figure 13A, B, and C illustrates three cases with very similar findings—namely, gastric folds extending through a somewhat wide hiatus directly into the stomach below without any acute angulation with the fundus of the stomach. These folds extend proximally above the diaphragm for a variable distance and often appear more prominent on the right and posterior aspect. During certain phases of swallowing, a small pouch may be noticed in association with these folds, and, in deep inspiration, this pouch and the phrenic ampulla above appear to form a single, distensible, sac-like structure (Fig. 14A, B, C). Little or no evidence of sphincteric action is noted at the junction of the folds with the phrenic ampulla. In two cases of this type, esophagoscopy showed the esophagogastric junction to be definitely above the level of the hiatus of the diaphragm.

As a working hypothesis, we have interpreted these findings as a failure of development of normal fixation of the esophi-

agus to the diaphragm. In the newborn and the infant, the cuff-like fascial attachments of the esophagogastric junction to the diaphragm at the hiatus—the so-called phrenicoesophageal membrane or ligament—are said to be unusually long or loose, permitting considerable



Fig. 15. Short esophagus with symmetrical, somewhat triangular gastric pouch; wide hiatus. Congenitally short esophagus?

mobility of the esophagus in relationship to the diaphragm (13). This is apparently required in order to facilitate the abrupt lengthening of the esophagus which occurs at birth when the lungs expand and the diaphragm sinks. Normal postnatal development of these attachments must be integrated with the development of the adult-size hiatus and of the fundus of the stomach. Persistence of a relatively wide hiatus with loose attachments of the esophagogastric junction to the diaphragm and a poorly developed fundus of the stomach might then be referred to as the "infantile type" of short esophagus or perhaps the "fixation-failure" type. Under normal circumstances, in the pres-

ence of these anatomical features, the esophagogastric junction will be found above the hiatus. Under anesthesia or at necropsy, with esophageal relaxation and equalization of pressure above and below the diaphragm, the esophagogastric junction is likely to be at or below the hiatus. The clinical significance of this failure of normal development appears to be that it predisposes to regurgitation and therefore to marginal ulceration, and perhaps also to the superimposition of a pulsion type of hernia. Once a pulsion hernia is superimposed on this type of developmentally short esophagus, the original roentgen manifestations are totally obscured.

The hypothesis that the stenotic variety of marginal ulcer with short esophagus is a later stage of the non-stenotic type is an attractive one. No clear-cut transition, however, from one to the other has been observed.² The possibility that the precursor stages of the stenotic variety may not be a pulsion hernia but rather the infantile type of short esophagus must therefore also be considered.

One might postulate that atypical varieties of hiatus hernia may be due to unusual traction from above by longitudinal spasm of the esophagus. The size of such sacs would be markedly limited, however, unless the phrenico-esophageal membrane was also damaged (7). If such damage were to occur, it is likely that pulsion would be a considerably more potent factor than traction. "Pulsion," of course, refers to the pressure differences below and above the hiatus, so that the effect of the "negative" pressure in the mediastinum is included in this term.

The possibility that minor degrees of true "congenitally" short esophagus, that is, partial thoracic stomach, are more frequent than many believe cannot be simply excluded (21). Such cases might also be

² Since this was written, a case has been observed in which the transition from the non-stenotic appearance to the stenotic variety was observed in clear-cut fashion. This case also demonstrated that the configuration of the hernial sac was triangular when outlined by barium entering from above through the stenosis but globular when filled from below by reflux from the stomach in the Trendelenburg position.

prone to the development of regurgitation, due to an associated wide hiatus and, therefore, to marginal ulceration. In such cases the esophagus would be short *per se* and not simply because its loose attachments to the diaphragm permit it to shorten to a limited degree. It might be impossible to identify such cases because of the great difficulty in defining the true length of the esophagus (6). Even if the esophagus were short on a congenital basis "in vivo," it might relax sufficiently under anesthesia or at necropsy so that its "true" length could not be determined. During routine gastrointestinal examinations, an occasional case of short esophagus (Fig. 15) is seen in which the gastric pouch is symmetrically situated in respect to the esophagus above and in which the configuration of the pouch does not suggest that it is pulsion in character or due to an "epiphrenic bell" (5). The occurrence of a congenitally short esophagus might be suggested in such cases, but confirmation is impossible to obtain.

The possibility that ectopic islands of gastric epithelium in the lower end of the esophagus may be the cause of marginal ulceration has been suggested by several authors (6, 20). This would not, however, explain the fact that herniation and regurgitation are present almost invariably in this condition. In the present series, the presence of gastric pouches lined by gastric mucosa rather than discrete islands of gastric epithelium has been demonstrated. There may, however, be an occasional case of peptic ulcer of the esophagus associated with ectopic epithelium. It is possible that the rare case without herniation might be explained upon this basis.

There are also rare instances in which a large portion of the esophagus apparently is lined by gastric epithelium (6). Such cases are designated as "heterotopic gastric mucosa" in the esophagus. This type of anomaly, as well as extensive partial thoracic stomach, would presumably also be prone to the development of marginal ulceration.

DISCUSSION

For reasons noted above, it is assumed that the precursory stages of marginal ulceration include the presence of a hiatus hernia of some type—that is, the esophagus is short before the development of a marginal ulcer. It should be noted, however, that additional esophageal shortening does occur after the development of a marginal ulcer, particularly of the stenotic type. It is not clear whether this is the result of a progressive fibrosis or increasing longitudinal spasm overcoming the fascial attachments to the diaphragm. In one case in the present group, a shortening of 10 cm. was observed over a period of ten years on repeated esophagoscopy examination and biopsy of the esophagogastric junction.

It must be noted that the fact that the esophagus is short on roentgen examination and esophagoscopy does not indicate that, at surgical exploration, it will be impossible to place the esophagogastric junction below the diaphragm. Sweet (22) states that he was able to reduce with ease 97 out of 111 cases of short esophagus with pulsion hiatus hernias. When, however, marginal ulceration with a cicatricial stenosis is present, it is not likely that reduction of the hernia will prove to be feasible (4).

In the present series, the roentgen findings described above have always been associated with active ulceration. With medical therapy and instrumental dilatation, the stenosis may become less marked, the ulcer patch less distinct, and the narrowing indicative of esophagitis may disappear. Restitution to a normal appearance has, however, not been observed either on roentgen examination or on esophagoscopy. It is conceivable, however, that an esophagitis with or without a marginal ulceration may go on to healing if gastric acidity is reduced. Such acid reduction may occur physiologically after the newborn period or as the individual ages. In the "healed" stage, as a result of fibrosis, a narrowed segment may persist. Cases of "congenital stenosis" at the esoph-

agogastric junction with a hiatus hernia in children, such as those described by Findlay and Kelly (9), may be explained in this fashion. A case described by Rennie *et al.* (18) indicates that narrowing may persist in the absence of fibrous stenosis or active ulceration.

Since treatment of marginal ulceration by either medical or surgical methods is difficult, the possibility of prophylaxis by early surgical intervention must be seriously considered. The presence of free regurgitation of acid gastric juice would then be an indication for surgical exploration in an attempt to reduce the hernia and to reconstruct the hiatus. It is not possible, however, at the present time to predict what fraction of such cases will go on to the development of a marginal ulcer.

DIFFERENTIAL DIAGNOSIS

"Peptic esophagitis": As pointed out above, in association with marginal ulceration, there is usually an esophagitis, presumably also peptic in nature. However, "peptic esophagitis" may occur apparently as a clinical entity and independent of a short esophagus or hiatus hernia. In 1935, Winkelstein (23) described "peptic esophagitis" as being associated frequently with duodenal or gastric ulcer with high gastric acidity. In contrast to marginal ulcer, which is associated with regurgitation and herniation, peptic esophagitis of this type may result from persistent vomiting of highly acid gastric contents, as in pyloric obstruction, in the early postnatal period, or in pregnancy, or it may occur as a result of the trauma and reflux due to an indwelling suction tube in the stomach. In peptic esophagitis, there is an ulcerative inflammatory process in the esophageal mucosa extending from the esophagogastric junction proximally for a considerable distance, at least 5 cm. and frequently 10 cm. Multiple erosions and irregular ulcerations are scattered at random throughout the involved segment. The esophageal lumen for the entire length of this segment is uniformly narrowed. This



Fig. 16. Peptic esophagitis after Levin tube intubation; duodenal ulcer. In its lowermost 9 cm. the esophagus is markedly narrowed in uniform fashion, with irregular margins and obliteration of mucosal pattern. Very small "traction" hiatus hernia.

is in contrast to marginal peptic ulcer in which the narrowed junctional segment is short, rarely exceeding 1 cm. A very small tent-like hiatus hernia may be associated with long-standing peptic esophagitis but appears to be incidental to persistent longitudinal spasm of the inflamed esophagus over a considerable period of time. Minor degrees of esophagitis, unassociated with narrowing, are very difficult to identify roentgenologically.

The roentgen findings in typical severe peptic esophagitis (Fig. 16) correspond to the pathological changes noted above. A long segment of narrowing, usually marked, is demonstrable in the lower esophagus, extending to the cardia. Even after dilatation, when filling of this segment is feasible, a long, uniformly narrowed segment is seen rather than a herniated gastric pouch. Spasm of the segment as a whole may be evidenced by changes in

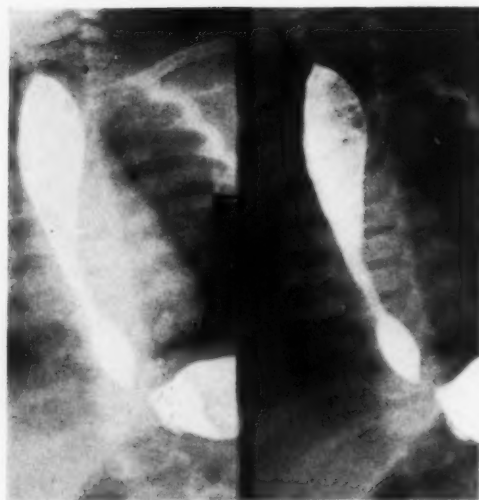


Fig. 17. Peptic esophagitis in an infant of three months. Long, uniformly narrowed segment of esophagus. The small sac above the diaphragm probably is a gastric pouch.

caliber on repeated examination. The mucosal pattern is obliterated and has a very irregular appearance, though discrete projecting ulcer pockets or craters are not seen. The margins of the narrowed segment show a spiculation or a fine serration and irregularity. Above, the esophagus is only slightly or moderately dilated and the transition to the narrowed segment is in a smooth conical fashion. With healing, a relatively smooth, symmetrical narrowed segment with parallel side walls, usually exceeding 1 cm. in length and located immediately above the esophagogastric junction, may be produced. Since the original cause may be temporary, healing is more common in peptic esophagitis than in marginal ulcer.

The direct etiologic agent in peptic esophagitis and marginal peptic ulcer is presumably the same—namely, the action of acid gastric juice on the esophageal mucosa. The different pathological findings may be due to quantitative differences in acid concentration, the trauma of intubation, and the duration and extent of contact of the acid gastric juice with the esophageal mucosa. At any rate, because of the different clinical, roentgen, and esoph-

agoscopic findings, these two conditions in the adult may be considered to be separate but related clinical entities. In infants (Fig. 17), a distinction between marginal ulcer with short esophagus and peptic esophagitis is probably not meaningful.

It is possible, in an individual with a hiatus hernia and short esophagus, for a diffuse ulcerative process of considerable length to develop in the lower esophagus, in contrast to a marginal, *i.e.*, a localized, ulceration at the esophagogastric junction. In the absence of a duodenal ulcer (or some other cause of high gastric acidity) or a history of intubation, this appears to be quite rare. We have seen three instances of this combination, and in two of them a definite duodenal ulcer was present.

Cardiospasm: In a typical case of cardiospasm, differential diagnosis from marginal ulceration is not difficult. In cardiospasm, the narrowed segment is characteristically beak-shaped and located within the esophageal hiatus of the diaphragm. A hiatus hernia is not present. The esophagus is dilated and redundant and extends to the right side of the mediastinum. When dilatation is less marked, irregular tertiary contractions are prominent. In an occasional case of cardiospasm without great dilatation, the narrowed segment may appear unusually high as compared with the levels of the diaphragmatic domes. In such cases, however, it can usually be demonstrated by studies in inspiration and expiration that the narrowed segment is truly within the hiatus. The beak-like narrowed segment will be cut off on deep inspiration but fill out in typical fashion on expiration. The mucosal pattern in the narrowed segment is intact. In a questionable case, administration of nitrites may be of aid. Esophagoscopy is conclusive in making this differential diagnosis.

Spasm of the Cardia: Occasionally, in association with a hiatus hernia, spasm of the cardia is said to occur. This can be differentiated from marginal ulcer roentgenologically by the smooth and inconstant character of the narrowing at the esophagogastric junction, the occurrence

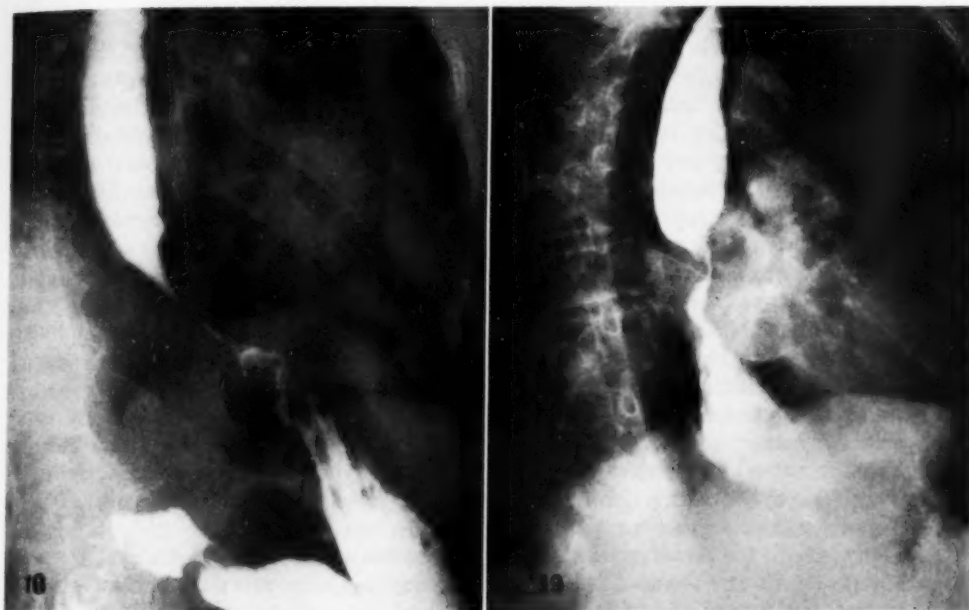


Fig. 18. Carcinoma of the gastric fundus extending submucosally into the lower end of the esophagus. There are no overhanging edges but the narrowed segment is rigid. No hernia. Soft-tissue mass in fundus.

Fig. 19. Recurrent carcinoma after esophagogastrectomy. Rigid angular narrowing with large soft-tissue mass. Eccentric overhanging edge and mucosal destruction.

of irregular tertiary contractions in the lower end of the esophagus, the fact that the hernia is not triangular in configuration nor the lower end of the esophagus fusiform and that the mucosal pattern is intact. Regurgitation is not likely to be present, and relaxation after nitrites is said to be common.

"Chalasia" of the Cardia: As noted above, it is not unusual to find in older persons a hiatus hernia and short esophagus with a patulous esophagogastric junction and marked regurgitation. Unless an ulcer patch is demonstrated or a definite segment with straight or angular margins and absence or marked irregularity of the mucosal pattern is seen, the diagnosis of an associated marginal ulcer cannot be made with any certainty. If clinical symptoms are severe or bleeding is a problem, esophagoscopy is necessary for an unequivocal diagnosis. Chalasia of the cardia in infants, as described by Neuhauser and Berenberg (15), may be associated with marginal ulceration. A case is illustrated

by Johnstone (13) under the title of "patulous cardia and idiopathic dilatation of the esophagus" which shows the roentgen findings described above for the non-stenotic group of cases of marginal ulcer.

Carcinoma of the Cardia: In a typical case of carcinoma of the fundus of the stomach involving the lower end of the esophagus, in which the mass in the fundus is clearly demonstrated and the esophageal extension has sharp overhanging edges, differential diagnosis from marginal ulceration is not difficult. Unfortunately, however, there are many cases of carcinoma arising in the region of the cardia in which an intragastric mass may be difficult to demonstrate and in which the esophageal extension may be submucosal and not produce any abrupt transition or sharp edge. Since the hernial sac cannot be distended in some cases of marginal ulceration with marked stenosis, the appearance of these two conditions may be quite similar. Differentiation is considerably more difficult if this type of

carcinoma arises in a pre-existing hiatus hernia. One must search for the slightest suggestion of the changes characteristic of carcinoma, namely, marked rigidity, irregularity or eccentricity in the course of the narrowed segment, asymmetrical involvement, a constant sudden change or step in one margin, abrupt transition to perfectly normal mucosal pattern, constant filling defects, or a small irregular area showing total destruction of the mucosal pattern (Fig. 18). If, in the absence of marked stenosis, free regurgitation is not demonstrable, carcinoma is much more likely than marginal ulcer. All such cases require esophagoscopy and biopsy.

Simple Stricture of the Esophagus: Benign strictures of the esophagus of unknown etiology have been reported at almost every site in the esophagus. These are usually fairly short narrowed segments with smooth margins, no overhanging edges, concentric in position and symmetrical in appearance. The esophagus above may be slightly or moderately dilated but appears normal in all other respects. The transition from the strictured segment to normal esophagus both above and below is usually abrupt and rarely conical. The mucosal pattern is intact. A common location for such strictures is said to be about 5 or 6 cm. above the hiatus (13). As noted above, it seems likely that a certain number of such cases would show gastric mucosa immediately below the stricture if sufficiently detailed study could be carried out. This group would then represent healed marginal ulceration or peptic esophagitis.

Scleroderma: Changes similar to marginal ulceration, or rather peptic esophagitis, have been reported as occurring in scleroderma. These changes are distinct from the more common findings in scleroderma involving the esophagus, namely, a lack of normal peristalsis, a flaccidity of the esophagus, and delay in the passage of barium into the stomach without any evidence of organic obstruction. When peptic esophagitis occurs, it must be assumed that sclerodermatous infiltration

of the cardia has resulted in regurgitation.

Corrosive Strictures: During the acute phase of an extensive stricture, the appearance may be identical with peptic esophagitis but does not resemble marginal ulcer. After healing, a fixed stricture may remain, but this may not extend to the esophagogastric junction and is usually of considerable length. A hiatus hernia is rarely identified and regurgitation is absent.

Esophagogastrostomy: After esophagogastrostomy and a surgically produced hiatus hernia, regurgitation is a common phenomenon. An ulcer in the lower end of the esophagus will occur in a certain number of such cases, with free acid in the gastric juice. This has been particularly troublesome in patients who have had anastomoses for cardiospasm. The roentgen findings may resemble those described above for marginal ulcer but are usually more bizarre because of operative deformity. The presence of stenosis at the anastomosis, however, cannot be assumed to be due to a marginal ulcer, since it may be operative in nature or due to recurrent disease (Fig. 19).

SYMPTOMATOLOGY

Of the series of 29 cases upon which the present report is based, 27 occurred in adults, 1 in a boy thirteen years of age, and another in an infant of nine months. Of the 27 adults, 5 were between the ages of forty and fifty, 8 between fifty and sixty, 10 between sixty and seventy, and 4 between seventy and eighty. The single case in infancy does not represent the true relative incidence at that early age but is due to the fact that our experience in this group is limited. Twenty-two cases were classified as stenotic and 7 as non-stenotic.

The patients in both groups complained of heartburn, which in every instance was related to posture. In many cases, it occurred in the middle of the night or on bending over, as, for example, to tie shoe laces. At times, the pain was agonizing and occasionally it radiated to the neck between the shoulder blades, or to such

unusual locations as the jaws and ears. Relief was frequently obtained by assumption of the erect position. Dysphagia occurred in 24 cases. This was usually not severe unless symptoms were of long standing. It was for the most part progressive, rarely episodic in nature, and in a majority of instances eventually required dilatation. In several cases the original symptom of heartburn became less marked as dysphagia increased.

Bleeding occurred in 8 patients. In 6, the bleeding was occult, but in 2 there was severe hemorrhage, requiring repeated transfusions. The majority of the patients with bleeding gave a history of repeated x-ray examination with consistently negative findings for duodenal and gastric ulcer.

In the present group, there was no case with an associated duodenal or gastric ulcer. This is somewhat at variance with other reports, which indicate that such an association is not infrequent. This may possibly be explained by the fact that we attempted to exclude cases of peptic esophagitis from our group of marginal ulceration.

There was no instance of perforation of the ulcer. As noted above, the ulceration was rarely of great depth.

It is unfortunate that satisfactory gastric analysis studies were not made. In general, such studies were considered to be contraindicated in the presence of marked esophageal stenosis. However, at esophagoscopy, the regurgitated gastric juice was always acid.

The fact that marginal ulceration may be confused clinically with arteriosclerotic heart disease was evident in 8 cases in which the original diagnosis was coronary occlusion or coronary insufficiency. However, electrocardiograms in this group were repeatedly negative.

TREATMENT

Treatment in the present series has been limited to symptomatic therapy and esophageal dilatation. We have had as yet no significant experience with surgical

intervention. Medical treatment has consisted in a strict ulcer regime with antacids and Banthine. This latter drug has occasionally relieved heartburn, apparently by producing a mild spasm at the cardia. Dysphagia, however, may be increased. The patient is advised to avoid those postural attitudes which cause regurgitation and to sleep with the head elevated.

Medical symptomatic treatment has rarely been satisfactory for any great length of time. With the onset of dysphagia, instrumental dilatation has been required. Esophagoscopy with bouginage and the use of a Hurst mercury-weighted tube have been recommended in both stenotic and non-stenotic cases if dysphagia was a prominent symptom. In the group with stenosis, progressive dilatation with Jackson bougies is required. In severe cases, esophagoscopy with dilatation may be necessary once or twice a week for several weeks until an adequate lumen, 30 to 36 French, is obtained. The patient is then instructed in the use of a Hurst mercury-weighted tube, which is passed twice a day before meals. As symptoms subside, the mercury-weighted tube is used less and less frequently until, in a majority of cases, a considerable free interval occurs during which no instrumental dilatation is required. Recurrence of symptoms after a variable period, perhaps months, is not infrequent, and repeated courses of instrumental dilatation may be required. In the most severe cases, with severe malnutrition, it may be necessary to introduce a Levin tube into the stomach for purposes of alimentation. This is a highly undesirable procedure but may tide the patient over a difficult period.

Surgical therapy of the stenotic group of cases of marginal ulceration requires esophagogastrrectomy. Unfortunately, however, a simple esophagogastrrectomy is frequently followed by regurgitation, and recurrent esophageal ulceration may be anticipated. A simultaneous vagotomy and resection of the acid-producing portion of the stomach have been recommended in order to produce an achlorhydria.

CASE REPORTS

CASE I: B. L., a 60-year-old married woman, entered the hospital complaining of heartburn of six months duration, occurring most often in the middle of the night, and dysphagia of two weeks duration. Three years prior to admission, a cholecystocolic fistula had been repaired and the patient had apparently made an uneventful recovery. Physical examination was negative except for two abdominal scars. Barium-meal study (Fig. 6A) revealed the presence of a stenotic segment 1 cm. in length in the region of the esophagogastric junction. A hiatus hernia 5 cm. long was present. The esophagus immediately above the stenotic segment was somewhat fusiform in shape, gradually widening into a moderate dilatation.

Esophagoscopy disclosed a whitish membrane covering the circumference of the esophagus at 31 cm. This was removed, revealing a markedly injected inflamed base. At 34 cm., the esophagus was narrowed by edematous mucosa. The lumen was dilated from 18 to 36 French without difficulty, after which the esophagoscope could be passed readily. Immediately distal to the stricture, gastric rugae were encountered. Regurgitation of gastric juice, acid to litmus, occurred. Biopsies from the narrowed segment revealed peptic ulceration. In the same section, one edge showed esophageal mucosa and the other gastric epithelium.

The symptoms improved after esophagoscopy and with the use of a Hurst mercury-weighted tube. Within a month, however, there was a recurrence of dysphagia, and esophagoscopy was repeated. A soft stricture was again encountered and was dilated. A whitish scab was seen at the site of the previous ulceration. A Levin tube was inserted, and through this the patient was fed for a period of two weeks. Roentgen examination after removal of the tube revealed findings essentially similar to those on the first examination, but a small hiatus hernia lined with gastric rugae was more definitely visualized below the strictured segment (Fig. 6B). Esophagoscopy two weeks after the removal of the Levin tube showed a very thin film of exudate, but the esophagoscope passed into the gastric pouch with ease. The patient was considerably improved and this improvement has been maintained at the time of this report for about eight months. She still complains, however, of some heartburn in the night, considerably relieved by elevating the head of the bed and by antacids.

CASE II: C. H., a 48-year-old woman, complained of heartburn and dysphagia. Her past history was essentially uneventful except for occasional heartburn of many years duration, especially after meals and most often in the middle

of the night and early morning. During the last six months, this symptom had become more severe, and the patient was placed on an ulcer regime, with very little relief. For the past two months she had experienced dysphagia to solid foods. Barium-meal examination performed elsewhere (Fig. 5A) had revealed marked obstruction 6 cm. above the diaphragm. The esophagus above the stenotic area was moderately dilated. The walls were not rigid. Insufficient barium passed the stenotic area to permit a study of the folds in this region. There was no definite evidence of an ulcer crater. Esophagoscopy revealed a stenosis at 33 cm., corresponding to the esophagogastric junction; the lumen measured about 5 mm. in diameter. On the left posterior lateral wall was an ulceration about 1 cm. in length. Dilatation to 36 French was done, and the esophagoscope was passed. Biopsy revealed intense acute inflammation. Repetition of the barium-meal examination (Fig. 5B) showed the stenotic segment to be only 4 mm. in length; a gastric pouch was present above the diaphragm. Esophagoscopy was again attempted three weeks later and again it proved impossible to pass a large esophagoscope readily until dilatation was performed to 36 French. During the next month, this procedure was twice repeated, with similar results. The patient left the hospital with continued dysphagia and heartburn. Introduction of a Hurst mercury-weighted tube before meals afforded some relief.

The patient was seen three months later for repeat esophagoscopy, which now revealed a stenosis at 31 cm. from the upper incisor teeth. Following dilatation up to 12 mm. or 36 French, the esophagoscope passed. An ulceration was not visible at this time. On leaving the hospital, the patient had only slight dysphagia. The heartburn, however, has continued. There is some relief with antacids and an anti-ulcer diet. The use of a Hurst mercury-weighted tube has been continued.

CASE III: M. B., a 53-year-old white male, experienced pain in the chest radiating to the back and side for three months. His past history was essentially negative. An electrocardiogram revealed no abnormality. The chest pain was persistent, especially after meals, and was not related to exertion. For two weeks before admission, he had difficulty in swallowing solid foods, accompanied by occasional heartburn. Barium-meal examination showed the esophagogastric junction to be located 6 cm. above the hiatus. It was constantly patulous and there was a relatively narrowed, incompletely distensible junctional segment almost 2 cm. in length, within which an amorphous patch of barium was seen (Figs. 11A and B). Esophagoscopy revealed retention in a dilated esophagus. At

37 cm., there was an area of ulceration measuring 2 cm. in length, with a whitish base and edges somewhat rolled. No stricture was noted. Fragments of esophagus and gastric tissue were obtained at biopsy, the former showing intense necrosis. The use of a mercury-weighted tube was recommended. The patient refused further treatment. Three months later, because of recurring dysphagia, heartburn, and pain in the chest, esophagoscopy was done elsewhere and a stenosis was found requiring progressive dilatation and the use of a Hurst mercury-weighted tube before meals. Considerable improvement followed this treatment. Re-examination by x-ray one year later, in another institution, for recurrence of dysphagia revealed a moderately narrowed cylindrical segment about 2 cm. in length at the esophagogastric junction. No ulcer crater was seen at this time. The patient was again placed on progressive dilatation and the use of a Hurst mercury-weighted tube before meals, with some improvement.

CASE IV: M. B., a 52-year-old white female, entered the hospital complaining of tarry stools and heartburn. The past history was essentially negative except for a hysterectomy at the age of forty for uterine fibroids. The present illness started three years ago with moderate burning pain behind the lower portion of the sternum, radiating into the neck. It came on especially when the patient was bending over, as in washing, or after a heavy meal. One month before admission, the pain became intense, and three weeks before admission tarry stools were first observed. These continued and on the day before admission to the hospital the patient fainted. On physical examination the only significant abnormality was the blood count: red cells 2,200,000, hemoglobin 7 gm., white cells 12,200 with a normal differential. The platelet count was normal. Four transfusions were administered during the period of a week. A barium-meal study (Fig. 10A and B) showed no obstruction to the passage of barium mixture, but the esophagogastric junction was located about 6 cm. above the hiatus and was patulous, with an angular border possibly due to an ulcer crater. The mucosal pattern in this region was absent. Regurgitation was marked. Esophagoscopy showed stomach contents in the upper esophagus, acid to litmus paper. The esophagus was moderately dilated, with a narrowing at 32 cm. The cardioesophageal junction was always patent but narrowed to about 6 mm. On the anterior wall was a whitish ulceration extending proximally for about 1.5 cm. and then encircling the left lateral wall of the esophagus. Below this region, gastric rugae were present. The lumen was dilated with bougies. The proximal esophageal mucosa appeared thickened and reddened. Biopsy revealed esophageal mucosa with peptic

ulceration. The patient was placed on an ulcer regime, and treatment with a Hurst mercury-weighted tube was instituted before meals. There has been considerable alleviation of her symptoms and no recurrence of gastrointestinal bleeding to date.

SUMMARY

(1) Short esophagus with esophagogastric or marginal ulceration is a clinical entity with characteristic roentgen and esophagoscopy findings.

(2) The roentgen features of two types of marginal ulceration, stenotic and non-stenotic, are described.

(3) The immediate cause of marginal ulceration is prolonged contact of acid gastric juice with the esophageal mucosa. This is made possible by regurgitation associated with a hiatus hernia.

(4) Both acquired shortening of the esophagus associated with a pulsion hernia and developmentally short esophagus may be precursors of marginal ulceration.

(5) "Peptic esophagitis" in the adult without a significant hiatus hernia may be differentiated from marginal ulceration with a short esophagus by the clinical, roentgen, and esophagoscopy findings.

(6) Differential diagnosis of marginal ulceration from carcinoma of the cardia may be extremely difficult and requires esophagoscopy and biopsy.

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SUMARIO

Esófago Corto con Ulceración Esofagagástrica o Marginal

El esófago corto con ulceración esofagagástrica o marginal representa una entidad clínica con típicas manifestaciones roentgenológicas y esofagoscópicas. Una serie de 29 casos forma la base de esta comunicación. En estos casos, había tres características constantes: 1. El esófago era corto y su unión con el estómago quedaba más arriba del hiato esofágico del diafragma. 2. Había reflujo o regurgitación libre del contenido gástrico al saco gástrico más arriba del diafragma. 3. Podía observarse ulceración de la unión esofagagástrica.

Roentgenográficamente, observáronse dos formas del estado: una, estenosada, con oclusión en el segmento marginal, y otra, menos común, no estenosada, sin estrechez absoluta ni tardanza en el paso del bario.

La regurgitación del contenido gástrico ácido al esófago es la causa inmediata de la ulceración marginal concomitante. Para la regurgitación, es indispensable que no haya obstáculo a la marcha retrógrada del contenido gástrico, bajo el influjo de la diferencia de presión en el abdomen y el

mediastino. Existen esas condiciones cuando un esófago recto y corto penetra directamente en un saco gástrico más arriba del diafragma, con un hiato ancho y falta de angulación aguda en la unión del esófago y del estómago. La insuficiencia de los esfínteres intrínseco y extrínseco en la unión esofagagástrica, sobrepuesta a dichas características anatómicas, da por resultado regurgitación.

Ya un acortamiento adquirido del esófago asociado con una hernia de pulsión o un esófago congénitamente corto pueden ser los precursores de la ulceración marginal.

Entre los estados que hay que diferenciar de la entidad aquí considerada figuran: esofagitis péptica, cardiospasma, relajación del cardias, carcinoma, estenosis simple y corrosiva del esófago, escleroderma y alteraciones incidentes a la gastroenterostomía.

Los síntomas sobresalientes del esófago corto con ulceración marginal son pirosis y disfagia de mayor o menor intensidad. En la serie de casos estudiada, el tratamiento se limitó a la terapéutica sintomática y la dilatación instrumental.

DISCUSSION

Laurence L. Robbins, M.D. (Boston, Mass.):

It is a pleasure to have the opportunity of discussing this paper. It presents a very interesting problem—one which, though not often encountered, is seen with sufficient frequency to afford us some knowledge of its complexities, including the fact that we have many things to learn in the future.

It seems to me that the authors make numerous assumptions that are at least difficult to prove. Although I have great respect for the esophagoscopes, I do not think we can rely on them without certain reservations. We have all had experiences in which we have found that the esophagoscopist is just as fallible as the radiologist. There is but one sure way of determining what is going on from the anatomical standpoint; that is to secure the complete specimen and have it studied adequately. A biopsy is important, but to determine whether a lesion is strictly marginal, a biopsy is not sufficient; anatomical examination of the entire specimen is necessary. We all know instances in which ectopic gastric mucosa in the esophagus was reported when actually merely the distal margin of the ulcer showed gastric mucosa. This is not proof that the ulcer is marginal. A comparable problem is in duodenal ulcer, in knowing precisely where the pylorus is. We are apt to rely for the answer more on the radiographic and fluoroscopic findings than on a description offered by someone else. Similarly, the roentgenologic evidence as to the location of the esophagogastric junction may prove extremely reliable. Here again, however, the final answer lies in careful studies of the entire specimen.

Certainly it should be remembered that, even when one is faced with the apparent entire syndrome—in other words, an esophageal ulcer or esophagitis, hiatus hernia, and duodenal ulcer—the appearance may be identical; and rarely what appears to be a simple benign esophageal lesion turns out to be a carcinoma. I do not wish to decry refinement of diagnosis, but it seems to me that the conditions shown have been made unnecessarily complicated. Too many subdivisions may defeat the purpose, as they are all probably a part of a single entity in which different variations of more or less the same process are going on.

Finally, I believe that not only is biopsy essential, but that in many cases it may be necessary to go beyond this and to explore, so that treatment as well as diagnosis may be accomplished.

Ross Golden, M.D. (New York, N. Y.):

I don't remember that Dr. Wolf mentioned irritability, a phenomenon associated with this condition. I have come to regard irritability as x-ray evidence of esophagitis. Sometimes this is so marked that the first bolus of barium, as it reaches the lower end of the esophagus, will be propelled back up toward the mouth. I don't know whether irritability can be taken correctly as evidence of esophagitis and would appreciate it if Dr. Wolf in closing would say something about it.

Dr. Wolf (closing): I agree that it is dangerous to take the word of the esophagoscopist as to his findings, without reservation, and I am sure that we cannot pin point these on the roentgen films. I can tell you, however, that a game is conducted during esophagoscopy in such cases, in which the esophagoscopist takes pieces of tissue, puts them in separate bottles, and predicts whether they will show gastric epithelium or esophageal epithelium, and for a particular individual the batting average is extremely high. I might repeat that, because of the belief of many that ectopic islands of gastric mucosa may be the common cause of marginal ulceration, we did in a number of cases take biopsies at several levels below the ulcer and found only gastric mucosa. This is not, of course, to say that ectopic gastric epithelium does not occur and may not be a cause of a similar or exactly the same condition. Nevertheless, the usual type of case is a combination of herniation, regurgitation, and marginal ulceration, we think, independent of ectopic islands of gastric mucosa.

I would like to emphasize again that in none of these cases were esophagoscopy and biopsy omitted. We think it is important not to make the unequivocal diagnosis of absence of carcinoma. I confess we have been fooled in at least one such case to date by believing a process benign which proved to be malignant. I think it is equally important, when atypical findings are present, not to make the unequivocal diagnosis of carcinoma because an incorrect extremely poor prognosis may then be given.

In answer to Dr. Golden, I would like to say that the examinations in these cases are necessarily tedious because of irritability in this region; that, frequently, incomplete filling occurs, apparently as a result of spasm. To get, for example, such roentgenograms as were shown, with good filling of the entire region, either with barium or air, may be extremely difficult.

Volvulus of the Cecum and Ascending Colon¹

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VOLVULUS OF THE cecum and ascending colon is not as rare as is generally assumed. The early recognition of this type of colonic obstruction is of great importance for radiologist and surgeon alike. The radiologist can make the diagnosis correctly in many instances, and on this basis the surgeon is guided to proper remedial procedures and, eventually, to prevention of a recurrence of such an accident.

Bundschuh (7) collected 110 cases of cecal volvulus in 1913. For the period 1913-42, Wolfer, Beaton, and Anson (63) collected 194 cases, bringing the total to 304. Courty (11) cites an additional 75 examples from France since 1940, and a review of the readily available sources in the American and British literature since 1942 has yielded 68 cases. To these we are adding 24 new cases, 19 of which were seen in a three-year interval, making a total of 471.

Volvulus of the cecum and ascending colon represents a type of mechanical obstruction of the proximal half of the colon, presupposing inadequate fixation of a variable length of the right colon complicated by pathologic degrees of rotation and displacement. The severity of obstruction varies greatly, depending on the extent and degree of torsion, displacement, and tension permitted to develop (time factor).

While the consensus of opinion as expressed in the literature is that a preoperative diagnosis of volvulus of the cecum and ascending colon is seldom made, the possibility of accurate diagnosis by radiographic means has been mentioned (5, 11, 12, 24, 43, 44, 51, 52, 58, 63).

ANATOMICAL CONSIDERATION

All modern writers agree that volvulus of the cecum is dependent on the failure of the primitive mesentery to become ad-

herent to the posterior abdominal wall. During its embryologic development the cecum assumes its normal position in the right iliac fossa by the operation of three processes: rotation, which carries the originally left-sided colon across the abdomen; descent, as a result of which the cecum sinks from a subhepatic position into the right iliac fossa; fixation, whereby the right mesocolon is obliterated and the right colon becomes adherent to the posterior wall of the abdomen. A mobile right colon represents an anomaly of fixation, the degree of mobility depending on the extent of the mesenteric attachment.

On the basis of 125 anatomic dissections, Wolfer *et al.* stress that not only must hypofixation (persistent common mesentery; imperfect fixation) of an adequate degree be present, but that some degree of hyperfixation of the ileum, cecum, or ascending colon is essential for the occurrence of volvulus. The point of fixation acts as a fulcrum on which the mobile segment can rotate, and its location will determine the length of right colon involved as a result of torsion. It may therefore be the principal factor determining the appearance and location of the twisted bowel and will partially account for the variability in the roentgenographic appearance.

While failure of fixation is recognized as the principal cause of a mobile right colon, this anomaly may be seen in association with non-rotation, partial rotation, and reversed rotation of the midgut or with an undescended or hyperdescended cecum or pelvic cecum. Rixford (52), Bulman (6), Carter (9), and Brady (3) have reported cases of non-rotation (left-sided colon) complicated by cecal volvulus. Dott (16), Donald (14), Holman (32), Norris (49), and Godfrey (25) have described reversed rotation of the colon (transverse colon passing posterior to the

¹ Accepted for publication in October 1952.

descending limb of the duodenum) leading to cecal volvulus.

CLINICAL CONSIDERATIONS

The exciting causes of volvulus of the cecum are not well understood. In the presence of the predisposing anatomical factors, the following have been suggested as precipitating causes: extremes in diet (coarse, undigestible vegetable fibers, explaining the greater frequency in European countries), over-exertion, sudden unusual physical activity, constipation, hyperperistalsis, and heavy purgation. Several cases of volvulus of the cecum in the postoperative abdomen have been reported (4, 12, 13, 44, 46). Abdominal tumors, traction by an inflamed appendix (29), mesenteric cysts (19), foreign bodies, chronic mesenteric adenitis, and typhoid fever have been implicated in isolated instances.

Volvulus complicating pregnancy or following immediately upon delivery has been reported with sufficient frequency that pregnancy should be considered an important exciting cause. Recent cases have been reported by Norris (49), Sheldon (56), Palmer (50), and Simons (57). The present series contains 2 cases occurring as a postpartum complication and one associated with a pregnancy of six to eight weeks. Explanations of the mechanism accounting for the volvulus in these cases are varied. Wolfer *et al.* quote Dreyer (17) and F  th and Obladen (22), who demonstrated upward displacement of a mobile cecum by the rising pregnant uterus, apparently confirmed by radiographic studies. It is not unreasonable to assume that the extreme state of restlessness of the patient in labor plays an important part in the causation of volvulus of the right colon in the presence of a mobile cecum, or that vomiting, which is a common accompaniment of early pregnancy, may precipitate torsion by inciting sudden mass peristaltic activity. Again, the possibility of sudden, violent movement as the precipitating cause must be considered.

Clinical manifestations of volvulus of

the right colon are those of an acute abdominal condition: sudden onset of pain, usually in the right lower quadrant, followed by abdominal distention, nausea, and vomiting. The degree of distention is extremely variable; however, the presence of a localized, bulging tympanitic mass anywhere in the abdomen should suggest the possibility of volvulus of the right colon.

ROENTGEN DIAGNOSIS

Generally speaking, volvulus of the right colon may manifest itself as an obstruction of complete or incomplete variety, *i.e.*, the colon distal to the point of torsion will be entirely or relatively devoid of gas and fecal matter or may contain such large quantities of gas that the exact site of obstruction cannot be localized on the preliminary scout films. In either case, the obstructed cecal segment may or may not show evidence of abnormal displacement.

Fortunately, the majority of cases demonstrate a combination of features permitting of accurate diagnosis, *i.e.*, in most instances of cecal torsion, the segment involved will be abnormally disposed within the abdominal cavity and the obstruction occurring at the point of torsion will be sufficiently complete that the colon distal to that point will be completely or almost completely devoid of gas and fecal matter.

Jakobsen (37) in 1945 stated that the typical roentgenograms of cecal volvulus show a greatly distended cecum, varying in size, with one or, less commonly, two fluid levels with the patient erect or in the lateral decubitus position. This unusually dilated segment of bowel containing gas and fluid is the feature which immediately strikes the observer's attention on reviewing the films. Ordinarily it is a fairly simple process to identify this structure as colon, and more specifically as cecum, if one remembers that in any obstructive process the bowel proximal to the site of obstruction will show evidence of gaseous and fluid distention, the degree of disten-

tion depending on the completeness of the obstruction, the interval elapsing since the onset of the process, and to a certain degree, on the competency of the ileocecal valve. If one then searches the right flank, and finds no evidence of distention there, *i.e.*, in the right colon, one must make a logical deduction and assume that the abnormally distended colonic segment represents the right colon which has twisted and become displaced to a remote part of the abdomen.

Complete Obstruction: The roentgenographic criteria for complete obstruction without displacement include (a) severe cecal distention with a normal disposition of the involved cecum and ascending colon in the right flank and lower abdomen; (b) absence (relative or complete) of gas and fecal contents in the colon distal to the site of obstruction; (c) ileus of varying degree involving the entire small bowel. Occasionally reversal of the lateral convex border of the cecum and ascending colon may suggest abnormal mobility and torsion of the right colon (see Case 6). Under these circumstances, one must assume torsion of 540 degrees or a multiple thereof. Serial studies of the abdomen may possibly demonstrate migration of the distended cecal segment to an ectopic position. Such mobility was observed in one of the cases of our series (Case 6).

Several examples of so-called axial torsion of the right colon have been described. In these cases the torsion is in the longitudinal axis of the bowel, with signs of complete obstruction but without displacement of the twisted segment. To account for the signs of complete obstruction in these cases, one must assume a torsion of at least 360 degrees.

Gross displacement of the cecum and ascending colon is a common finding in cases of complete obstruction due to cecal torsion. Several writers have stated that in 75 to 90 per cent of cases of cecal torsion the twisted cecum will be in the left upper abdominal quadrant. These figures, however, appear somewhat high. Ap-

proximately 40 per cent of our cases demonstrated such displacement.

In analyzing a large group of cases of volvulus of the right colon with gross displacement of the cecal segment, one finds that in a number of instances evidence of 180 degrees torsion has been obtained at surgery. In these it must be assumed that it is the tightness of the twist rather than the number of turns which determines the completeness of the obstruction. It must be recalled that hyperfixation is usually present at the site of torsion, and that a combination of these three factors—partial torsion, displacement, hyperfixation—will account for the signs of complete obstruction.

The location of the dilated cecal segment and its appearance on the roentgenogram are apparently related to the length of the right colon involved as a result of torsion and the extent to which the obstructed segment is dilated. If a short segment consisting of the cecum is involved, it will usually be found, distended with gas and fluid, in the right mid flank or right upper quadrant, although it may assume a position in the mid abdomen. It will be present as a rounded or ovoid segment of bowel which, because of its size, can safely be assumed to represent cecum, since the distal colon is usually deflated or contains only a small amount of gas and fecal matter. Haustral markings are lost because of the great pressure present in the obstructed short cecal segment, which functions as a closed loop in the presence of a competent ileocecal valve (Case 7).

When torsion occurs higher in the ascending colon, or a larger segment of right colon is involved, as in cases of hyperdescended cecum, the probability of an ectopic location of the distended right colon is markedly enhanced. Also, haustral markings are more readily identified as larger segments of right colon are involved, in spite of severe degrees of distention. (Cases 12 and 14)

Features usually demonstrated on the roentgenographic studies, regardless of the disposition of the involved colon, are

severe fluid and gaseous distention of the obstructed cecal segment; almost complete gaseous deflation of the colon distal to the site of obstruction or, at the most, demonstration of small amounts of gas and fecal matter. Usually, there is also considerable gaseous and fluid distention of the small bowel loops, with the small bowel occupying a variable location, frequently being found in the right flank to the right of the obstructed cecum.

Other features which have been mentioned in making the diagnosis and which should be sought are: absence of gas- and fecal-containing cecum in the normal location; observation of the ileocecal valve lying to the right of the distended viscus; a gradual narrowing of the gas-distended bowel to a cone (beautifully demonstrated in Cases 7 and 12), as seen on the plain film, suggesting twisting of the mucosa.

Certain problems are encountered in the analysis of the preliminary flat and upright studies which might confuse the observer. As previously stated, the striking feature in cases of volvulus of the right colon with displacement and with signs of complete obstruction is the presence of a greatly dilated segment of bowel with one or, less frequently, two fluid levels. The very size of this dilated segment will usually exclude consideration of small bowel. When the segment is rounded or ovoid and is located in the right mid flank, right upper quadrant, or mid abdomen, and no significant gaseous distention of the colon is identified, one can only conclude that it is the cecum.

If the ectopically located cecum and ascending colon are present in the left upper quadrant, which frequently occurs, the question of differentiation from the stomach arises. The size, shape, and configuration of the distended segment of colon rarely simulate perfectly a stomach distended with gas and fluid. The presence of haustral markings should suggest colon. The abnormally dilated segment will rarely demonstrate the intimate relationship to the left diaphragmatic leaf that the normal

stomach does, particularly in the upright position. Moreover, the upright abdominal study may show a fluid level within the stomach above the gas- and fluid-distended right colon. Nevertheless, in an occasional case, a twisted right colon high in the left upper quadrant will be so greatly distended that haustral markings are not identifiable and one is forced to consider the possibility of severe gastric dilatation or obstruction. Case 11 presented this problem, although we felt that a fluid level was identifiable within the stomach in the upright position. In such cases one can pass a gastric tube and, after aspirating the stomach, re-examine the abdomen, or one may have the patient swallow a small amount of barium and identify the stomach in this manner. If there is still doubt, one can finally examine the colon by means of a barium enema.

It might be wise to re-emphasize at this point the necessity of the upright study. Demonstration of a fluid level in an abnormally dilated segment of bowel directs attention to the pathology at hand. It is useful in permitting differentiation of a twisted right colon high in the left upper quadrant from the stomach. Occasionally the right colon which presents ectopically in the left upper quadrant may be misinterpreted as distal transverse colon and no significance may be attached to it unless attention is directed to it by the presence of a fluid level. This is particularly true in early cases of torsion where the degree of distention is not yet striking (see Cases 9 and 10). An isolated colonic segment containing gas and fluid should suggest the possibility of volvulus if features previously mentioned are identified.

Occasionally one may demonstrate change of position of a dilated cecal segment on successive progress studies. This abnormal mobility in the presence of roentgen signs of colonic obstruction should suggest torsion. This finding occurred in Cases 4 and 6.

With respect to the demonstration of abnormal mobility of a dilated but normally disposed cecal segment, it might be

wise to examine the abdomen in the right lateral decubitus or Trendelenburg position in an effort to cause the cecum to gravitate to an abnormal location. Ultimately, however, recourse to barium enema examination or surgery will be necessary for confirmation.

Incomplete Obstruction: A variable number of cases of volvulus of the right colon may be classified as producing signs of incomplete obstruction. In these cases the colon distal to the torsion contains gas and fecal matter in such quantity that it is impossible to localize the site of obstruction on the preliminary scout studies. Clinical experience has indicated that in these circumstances, the torsion amounts to one-half twist or 180 degrees, so that there is a simple reversal of the lateral border of the twisted right colon. Quite often in cases of this type there is no displacement of the twisted segment. Very possibly the incompleteness of the obstruction permits passage of gas into the distal colon and thus obscures the true picture (Cases 1 and 2).

The twisted cecum may be displaced medially, thus suggesting abnormal mobility or, occasionally, the distended cecal segment may lie transversely in the abdomen. As abnormal positions are assumed by the dilated cecum, the possibility of torsion should be entertained more seriously in spite of considerable gaseous distention of the colon distally.

In all cases, a rather marked cecal distention should suggest the diagnosis of partial torsion of the right colon, particularly if a fluid level is demonstrated in the upright or decubitus position, and especially if there is evidence of rapidly increasing cecal dilatation on progress studies. As greater degrees of displacement of the cecum are noted, there is a greater tendency for the colon distal to the site of obstruction to become completely or relatively devoid of gas and fecal contents.

In partial torsion (180 degrees) resulting in incomplete obstruction, the criteria for diagnosis may be summed up as follows: (a) Cecal torsion should always be con-

sidered when the degree of cecal distention is out of proportion to the dilatation of the remainder of the colon. (b) Considerable fluid is present within the cecum. (c) The cecum and ascending colon normally show a convex lateral border and a concave medial border, assuming a somewhat reniform appearance. Occasionally the twisted right colon maintains this reniform appearance in spite of severe distention. In that event, partial torsion may be suspected if it is possible to demonstrate that the medial border of the dilated right colon is convex and the lateral border concave. Obviously, for this finding to be present, a fairly large segment of the right colon must be involved (see Cases 3 and 6). (d) In several cases of partial torsion without displacement we have observed apparent discontinuity of the gas column slightly distal to the dilated cecal segment. We believe that this may indicate the point of torsion. Although corroborated surgically in several of our cases, this finding is inconstant, and its significance requires further evaluation. It has been seen also in association with severe ileus and colonic obstructions due to other causes. (e) Usually a variable degree of gaseous and fluid distention of the small bowel will be present.

For partial torsion (180 degrees) with signs of incomplete obstruction and displacement of the cecum, the same criteria prevail. As the degree of displacement becomes grossly obvious, abnormal mobility must be assumed and torsion considered.

It would be logical to assume that the most common type of torsion involving the right colon would consist of a 180-degree twist in a clockwise or counter clockwise direction, without obvious evidence of cecal displacement, and with signs of incomplete obstruction. As a high index of suspicion is maintained in cases fulfilling the criteria listed for this group, the number of cases of cecal volvulus observed should increase, and correspondingly the number of cases with displacement will decrease.

In every case where a diagnosis of prob-

able volvulus of the right colon has been made, confirmation by barium enema should be undertaken. Conization of the bowel lumen with spiral twisting will frequently be demonstrated. Rarely the obstruction will be fairly sharp, without gradual narrowing of the colonic lumen, and in such a case one might be confused, particularly if the colon has been filled into the region of the iliac fossa. The presence of a markedly distended segment of bowel in proximity to the apparent termination of the cecum should not be disregarded, but rather should alert the roentgenologist to the diagnosis of cecal volvulus.

DIFFERENTIAL DIAGNOSIS

In the presence of an ectopically located cecum resulting from torsion of the right colon, the roentgenographic appearance is fairly characteristic and can be simulated by only a few pathologic entities.

Partial torsion of the right colon with signs of incomplete colonic obstruction cannot be differentiated without contrast studies from severe generalized ileus or obstruction in the distal colon by carcinoma, inflammatory disease, adhesions, or bands. Partial torsion should be suspected when cecal distention is severe or progressive on serial studies, when the degree of distention of the remainder of the colon does not appear compatible with obstruction elsewhere in the colon, and when an apparent discontinuity is suggested in the ascending colon near the hepatic flexure in the presence of the other criteria listed. In cases of obstruction due to carcinoma, one usually sees considerable fecal matter throughout the colon proximal to the obstruction, and less often evidence of a fluid level in the cecum, unless the obstructing growth occurs in the proximal colon, in which case the cecal contents may be fluid in character.

Large intra-abdominal abscesses containing gas and fluid have constituted the single most difficult acute abdominal condition to differentiate from volvulus of the right colon. We have seen 3 cases of intra-abdominal abscess which resulted

from perforation of colonic diverticula in which the size and appearance of the abscess caused one to consider volvulus of the right colon. We have also seen a retroperitoneal abscess containing gas and fluid which developed secondary to nephrectomy for a hydronephrotic calculous kidney on the left, and which, being sharply localized to the renal bed, could cause some concern from the standpoint of differential diagnosis. Intra-abdominal abscesses should present a clinical picture of infection and toxemia. The course may also indicate a condition of some duration, whereas the pertinent radiographic features in cecal volvulus will develop in twenty-four hours or less.

Very rarely, reduplication of the colon may result in a large pocket containing gas and fecal matter, creating a bizarre picture which, depending on the location of the reduplicated segment, may have to be differentiated from cecal volvulus. In these cases the history will point to an abnormality of long standing, and barium enema studies should permit of accurate differentiation (31). Similarly, large blind intestinal pouches resulting from lateral anastomosis of small and large bowel may occasionally have to be differentiated.

Sigmoid volvulus presents, in most cases, a fairly characteristic roentgenographic appearance and should not cause any difficulty in differentiation. Severe degrees of ileus involving the entire intestinal tract, but particularly the colon, can result in marked degrees of cecal distention. Such cases cannot be differentiated from partial volvulus of the right colon with signs of incomplete obstruction without a barium enema study. Undoubtedly, the clinical features of a paralytic ileus should be of considerable help in differentiation.

CASE REPORTS

CASE 1: R. Z., a 65-year-old white female, was admitted Sept. 6, 1949, with abdominal pain and vomiting of ten days duration. Passage of gas and liquid stools had occurred throughout her present illness. She gave a history of "gallbladder attacks" in 1942, 1944, and 1947, with abdominal pain and

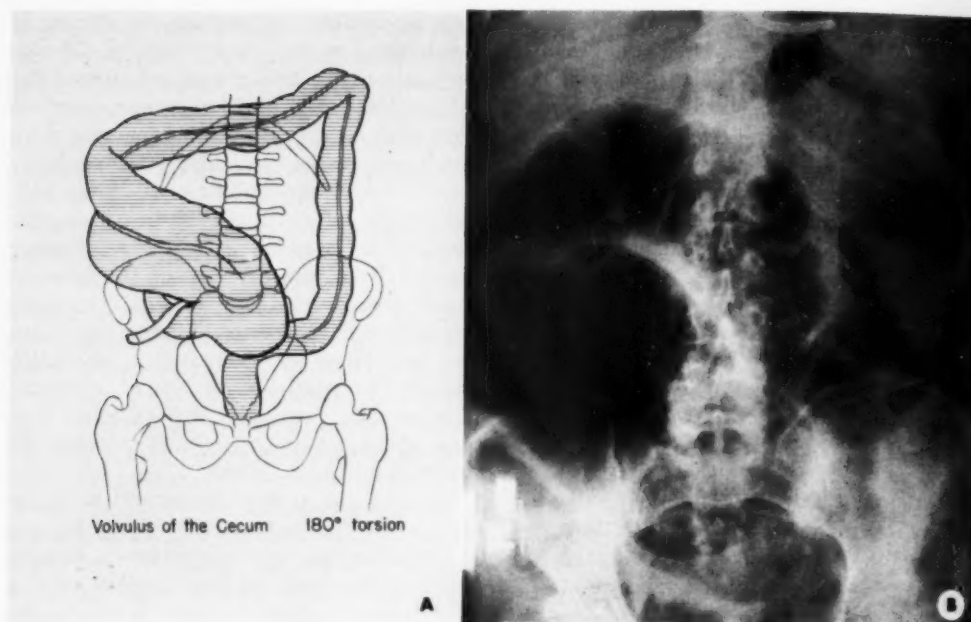


Fig. 1. Case 1.

bloating but without jaundice or clay-colored stools.

Scout films of the abdomen, Sept. 6, showed generalized gaseous distention of the colon, particularly the cecum, and of the small bowel (Fig. 1). Re-examination the following day revealed increasing cecal distention. A barium-enema study disclosed an obstruction in the ascending colon. A diagnosis of volvulus was made.

At emergency laparotomy a 180° clockwise rotation of the cecum was found, *i.e.* the lateral attachment was rotated anteriorly to the mid-line.

Comment: This case is illustrative of the fact that large amounts of gas may be seen throughout distal colonic segments in cases of partial torsion (180 degrees) without cecal displacement.

CASE 2: M. W., a 57-year-old woman, was admitted June 4, 1952, following a fall in which she sustained a compression fracture of the first lumbar vertebra. From June 5 to 10 she experienced nausea, abdominal cramps, and gradually increasing abdominal distention, leading to a clinical assumption of paralytic ileus.

A survey film of the abdomen on June 10 showed excessive distention of the cecum and loops of ileum. There was relatively little gas in the more distal colonic segments, with apparent discontinuity of gas in the mid ascending colon (Fig. 2A). A contrast study on June 11 demonstrated complete ob-

struction at this point (Fig. 2B). The radiologic diagnosis was: obstruction of the mid ascending colon, very likely resulting from cecal torsion; probable pneumoperitoneum.

At operation, June 11, a torsion of the cecum and lower ascending colon, 180° clockwise, was found at a point of fixation of the large bowel by multiple peritoneal adhesions. The patient died a few hours later.

Comment: Intermittent passage of some gas and liquid fecal matter lulled the clinician into the erroneous assumption of a post-traumatic ileus. Such an error must be guarded against by early and, if necessary, repeated radiologic examination.

CASE 3: D. V., a 59-year-old white male, was admitted on Oct. 3, 1952, with abdominal pain and distention of several days duration. A scout film of the abdomen showed severe distention of the cecum with reversal of the right colonic contours, small amounts of gas in the transverse colon, and moderate small bowel distention. The tentative diagnosis was partial torsion of the mid ascending colon with obstruction. With a barium enema, an obstruction was demonstrated in the mid ascending colon, with slight spill of barium into the obstructed cecal segment under continued pressure injection (Fig. 3A and B).

On surgical exploration a severely distended, freely

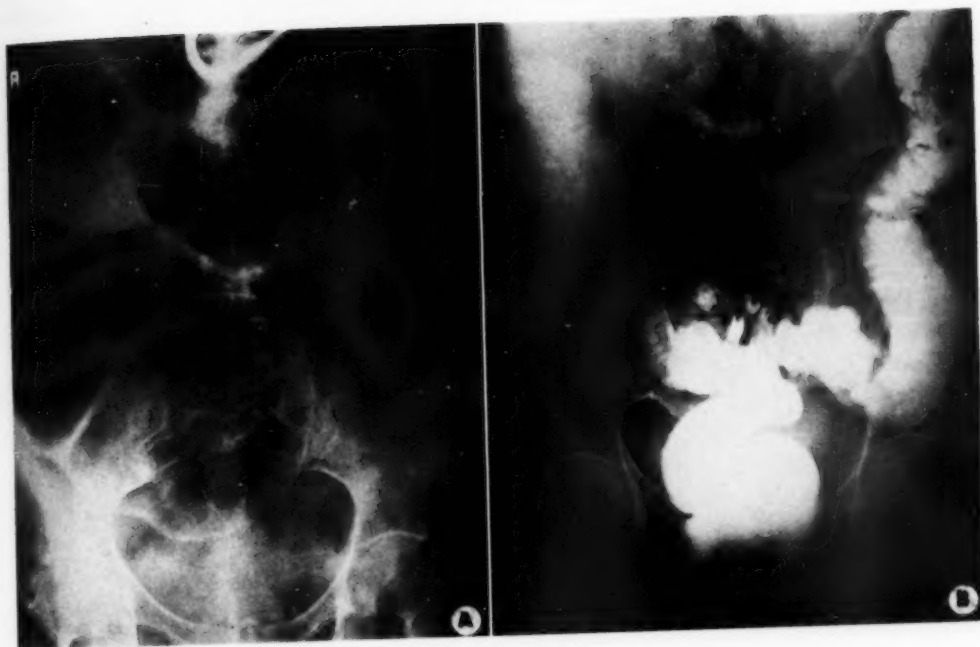
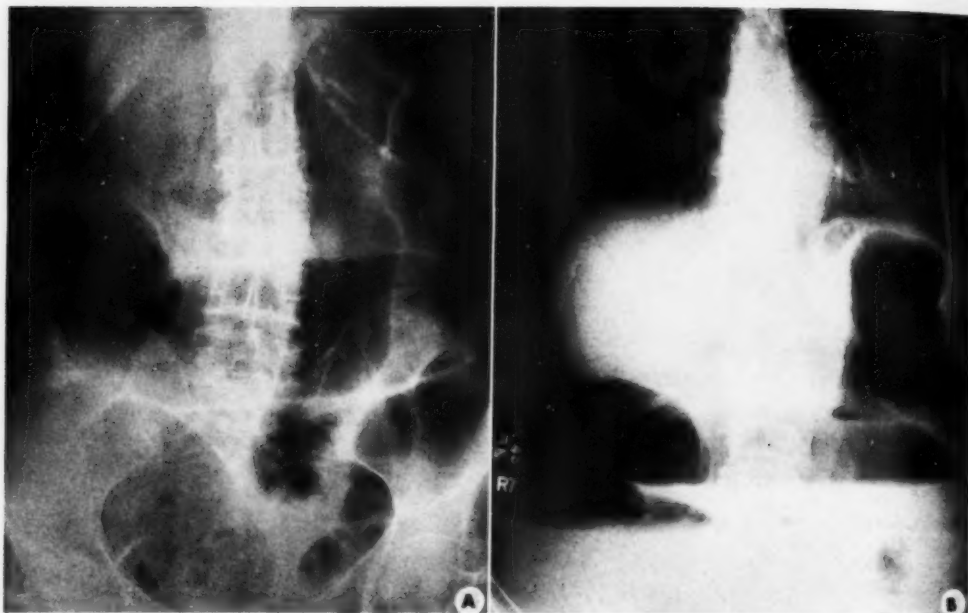


Fig. 2. Case 2.



Fig. 3. Case 3.



Figs. 4A and 4B. Case 4.

movable right colonic segment was found. The lateral border of the ascending colon was rotated anteriorly. A cecostomy was done. The patient was extremely uncooperative postoperatively and forcefully removed the cecostomy tube and the long tube. Death occurred on Nov. 3.

At autopsy the right mesocolon was found to be extremely long. Minimal inflation of the colon and severe ileus of the small bowel with peritonitis were present.

Comment: Particularly noteworthy in this case are the severe degree of right colonic distention and the reversal of right colonic contours. The latter finding is practically pathognomonic of torsion.

CASE 4: E. P., an 80-year-old woman, was admitted on April 21 after an illness of eight days, with abdominal distention, pain, and vomiting. A scout film of the abdomen on the day of admission showed marked distention of the cecum and of the ascending and transverse colon and splenic flexure, suggesting colonic obstruction just beyond the latter level. The cecum was in a relatively normal location (Fig. 4A and B). A survey film, April 27, revealed the following: excessive distention of the cecum, with migration of this segment to the mid abdomen; abnormal rotation of the cecum demonstrable by its kidney-shaped configuration, with the hilus-ileocecal junction directed caudally; moderate gas delineation of the transverse colon and splenic



Fig. 4C. Case 4.

flexure (Fig. 4C). Diagnosis: Partial obstruction in the most cephalic segment of the descending colon; volvulus of the cecum with shift to the mid abdomen.

At operation, April 28, the cecum was found to be rotated 180° clockwise, with the lateral border directed superiorly. A cecostomy was done. A month later an annular carcinoma was resected from the upper portion of the descending colon.

Comment: Cecal volvulus in this instance occurred under hospital observation following partial obstruction of the large bowel just beyond the splenic flexure. The volvulus had to be dealt with before the primary neoplastic obstructive colonic lesion could be taken care of.

CASE 5: H. G., a 57-year-old white female, was admitted Oct. 5, 1949, with abdominal distention and pain of eight days duration. Scout studies of the abdomen showed a distended cecum, presenting transversely in the mid abdomen, and a moderate amount of gas present in the remainder of the colon (Fig. 5).

On Oct. 6 the abdomen was explored. The cecum was hugely dilated and on the verge of rupture. It was rotated 180° and occupied a transverse position in the mid abdomen. Following deflation by means of a trocar, the cecum and distal ileum were exteriorized and subsequently resected. A barium enema study on Jan. 20, 1950, revealed no abnormalities of the colon in the area of exteriorization.

Comment: The abnormal location and tremendous, disproportionate distention of the cecum are indicative of torsion and displacement, provided other pathological conditions are excluded surgically and radiographically. Note again the large amounts of gas throughout remaining segments of the colon, indicating incomplete obstruction.

CASE 6: T. V., a 20-year-old white man, was admitted on Sept. 30, 1951, after an illness of three days duration, with severe abdominal distention, nausea, and vomiting. He was severely crippled by previous poliomyelitis.

A survey film of the abdomen, Oct. 1, showed an excessively distended cecum to the right of the lumbar spine, greatly distended ileal loops in the right upper abdomen, and distention of the distal colonic segments (Fig. 6B). On re-examination, Oct. 2, the abnormal conditions encountered were essentially identical with those of the preceding day. In addition, the distended cecum had migrated to the epigastric area (Fig. 6C). A contrast study disclosed severe obstruction in the ascending colon. The cecum had returned to the location originally observed, and the ileocecal junction was assumed to be located at the lateral cecal margin (transposition) (Fig. 6D).



Fig. 5. Case 5.

On surgical exploration on the same day, a severe cecal volvulus with a torsion of approximately 540° was corrected. Marked fixation of the upper ascending colon by peritoneal bands was relieved.

Comment: This case presents all the characteristic evidences of cecal volvulus: excessive distention of cecum and distal ileum, reversal of the cecal borders, abnormal migration of the cecum as observed on successive days, obstruction in the ascending colon demonstrated on contrast study.

CASE 7: D. G., a 61-year-old male, was admitted on Sept. 23, 1950, with abdominal cramping and constipation of four days duration and vomiting during the past twelve hours. In December 1947, a survey film of the abdomen had revealed a moderate colonic distention with a transversely placed cecum located in the midline at the level of the umbilicus. In January 1948, a barium enema study had demonstrated a short, mobile cecal segment similarly placed in the abdomen.

A scout film on Sept. 23, 1950, showed a distended cecal segment in the right mid flank, small bowel distention, and absence of gas in the distal colon (Fig. 7B and C). A contrast study revealed an obstruction in the lower ascending colon (Fig. 7D). The radiologic diagnosis was volvulus of the cecum with complete obstruction.

Surgical exploration revealed volvulus of a mobile cecum around an omental band across the terminal

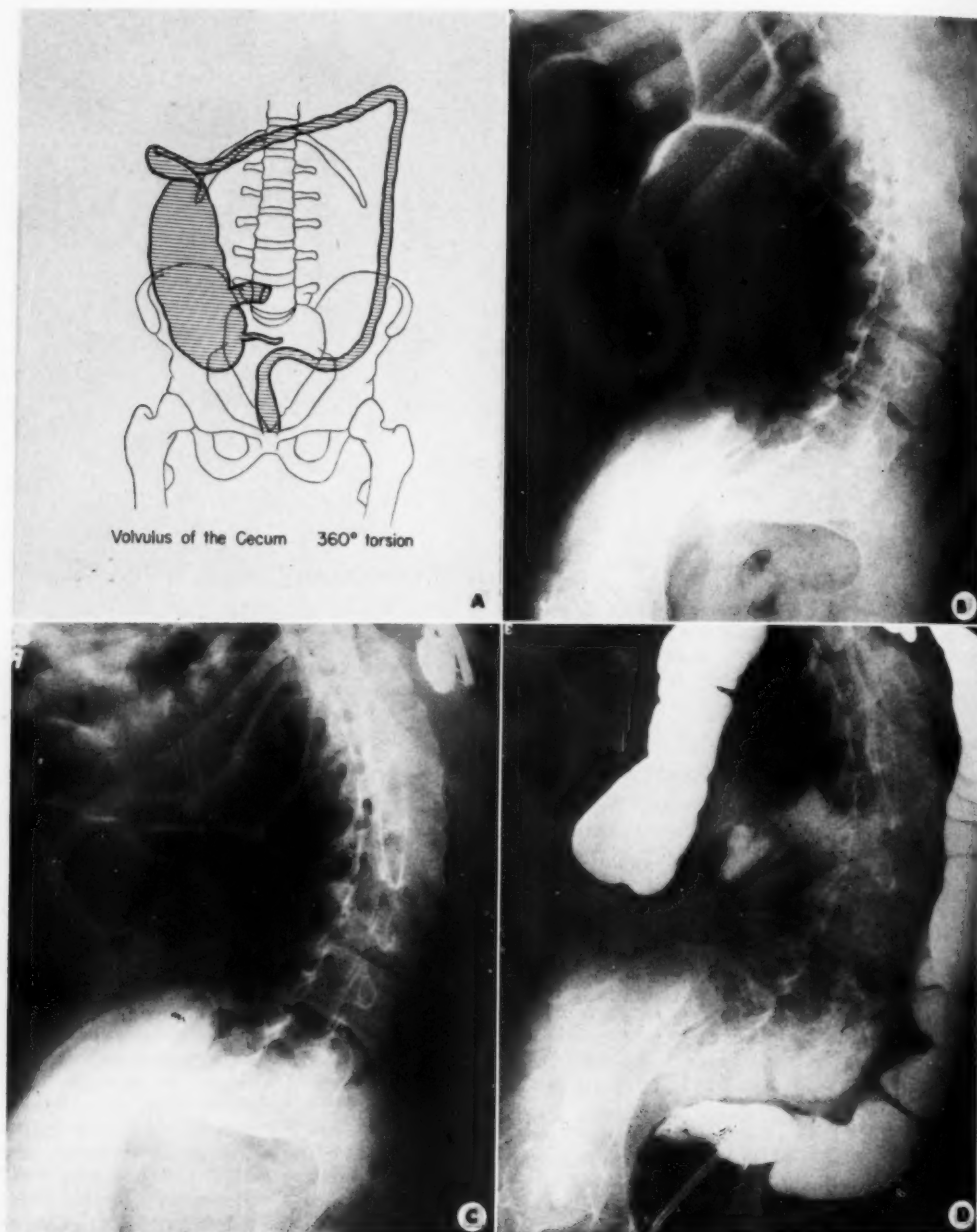


Fig 6. Case 6.

ileum. Right colectomy and ileotransverse colostomy were done and the patient was discharged on Oct. 25.

Comment: Demonstration of an abnormally mobile cecum in the presence of

vague abdominal symptoms suggesting incomplete or recurrent bouts of intestinal obstruction should suggest the possibility of subacute or recurrent volvulus of the cecum. The shorter the involved seg-

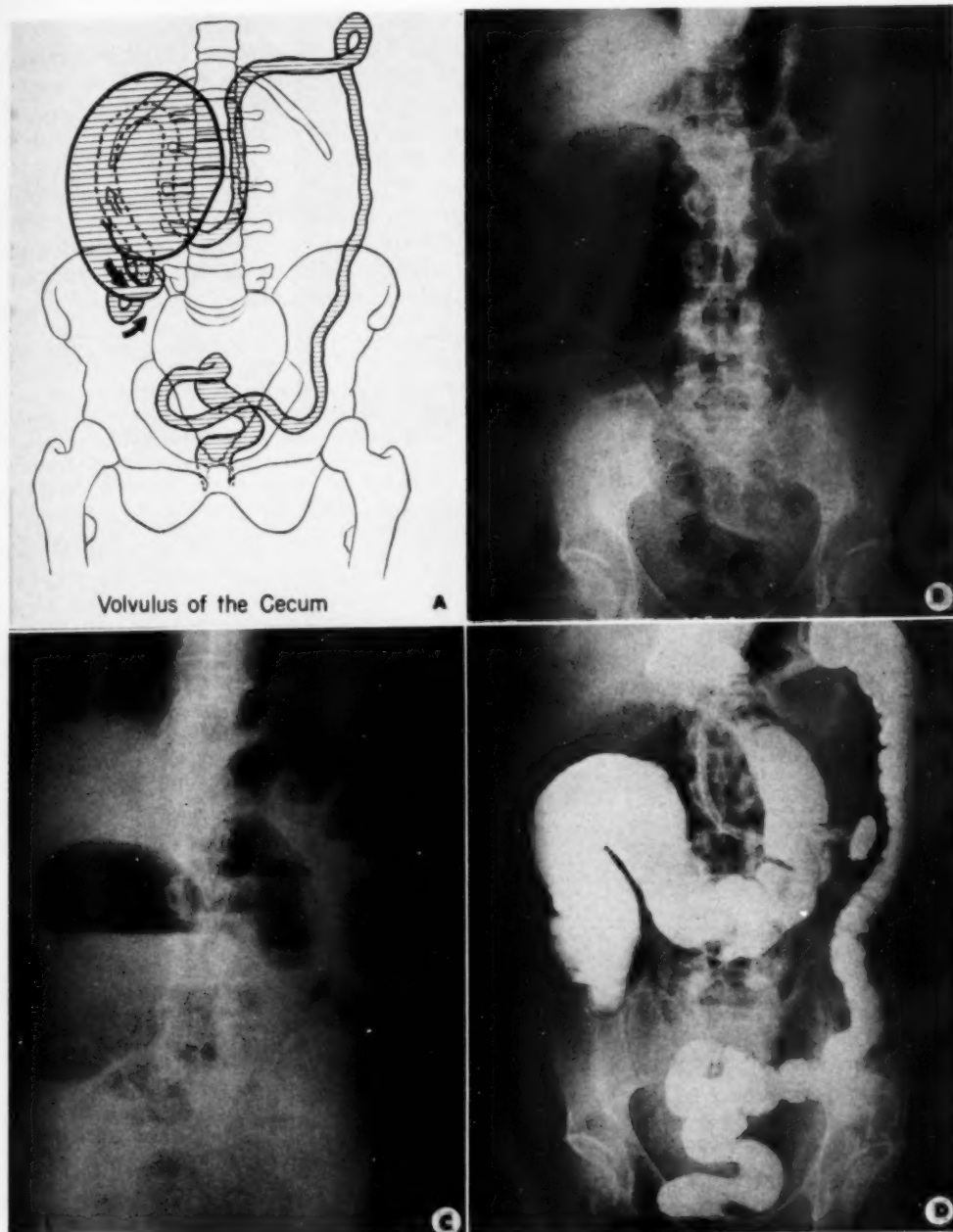


Fig. 7. Case 7.

ment in cases of volvulus of the right colon, the more apt is there to be a loss of haustration and the more likely is it that the dilated cecum will be located in the right

abdomen. Obviously, a short segment cannot be displaced to a remote position.

CASE 8: B. D., a 24-year-old female, was admitted on April 5, 1948, with abdominal pain,



Fig. 8. Case 8.

nausea, and vomiting of three days duration. A scout film of the abdomen revealed localized colonic distention in the upper right and mid abdomen with a short distended ileal segment.

At surgery the cecum and ascending colon were found to be greatly distended, freely movable, and located in the right upper abdomen. In addition, dense adhesive bands were found across the mid ascending colon. The bands were severed, and an inflamed appendix was removed.

Comment: Note the localized colonic distention in the right upper quadrant, with the cecal base presenting in the mid-line at the level of the umbilicus. The ileocecal junction is beautifully outlined by gas, at the right lateral aspect of the cecum. Note, also, the absence of gaseous or fluid distention of the right colon in its normally anticipated position (Fig. 8).

If the obstruction were in the mid transverse colon, as might be suspected, then one should anticipate gaseous and fluid distention of the entire colon proximal to the obstruction. The absence of this can only lead to the conclusion of torsion and displacement. In our opinion, adhesive bands will rarely produce obstruction of the colon. Surgical or roentgenographic

evidence of an obstructive process in the right colon should always suggest volvulus as the etiologic basis when there is evidence of abnormal mobility of the cecum and ascending colon, especially when other causes are excluded surgically. Adhesive bands are contributory to the obstructive process only in that they provide a point of hyperfixation. It is a combination of torsion, displacement, and hyperfixation that accounts for the obstruction.

CASE 9: E. K., a 21-year-old man, was admitted on Nov. 17, 1950, with uninterrupted severe, generalized cramping abdominal pain for the past twelve to fifteen hours, with nausea, and beginning vomiting. Previous mild attacks of similar nature had subsided spontaneously without hospitalization.

A radiologic survey of the abdomen showed a moderately distended colonic segment in the left upper abdominal quadrant, some gas in colonic segments along the left flank, and a few mildly distended small bowel loops in the left upper abdomen. There was conspicuous absence of inflated intestinal segments along the entire right flank and especially the right iliac fossa (Fig. 9B). The tentative diagnosis was volvulus of the cecum with faulty anatomic orientation and marked displacement. A contrast study of the colon confirmed this impression and demonstrated readily the point of torsion overlying the third lumbar vertebra (Fig. 9C).

Surgical exploration was undertaken, and the cecal volvulus was corrected, with fixation of the cecum and ascending colon in their normal location along the right lateral abdominal wall. The patient was discharged six days later after an uneventful recovery.

Comment: The radiologic study disclosed completely the cardinal points of cecal volvulus and guided the surgeon to a remedial procedure.

CASE 10: J. J., a 40-year-old colored male, was admitted on Aug. 12, 1945, with severe generalized cramping abdominal pain of eighteen hours duration. Anteroposterior and upright roentgen studies of the abdomen were interpreted as showing marked gaseous and fluid distention of the stomach.

Operation, on Aug. 13, consisted in detorsion of a volvulus of the ascending colon with a viable cecum presenting high in the left upper quadrant and removal of a gangrenous appendix.

Comment: Note the presence of haustrations and fluid level in the cecum, which is seen in the left upper quadrant. The absence of an intimate relationship to the

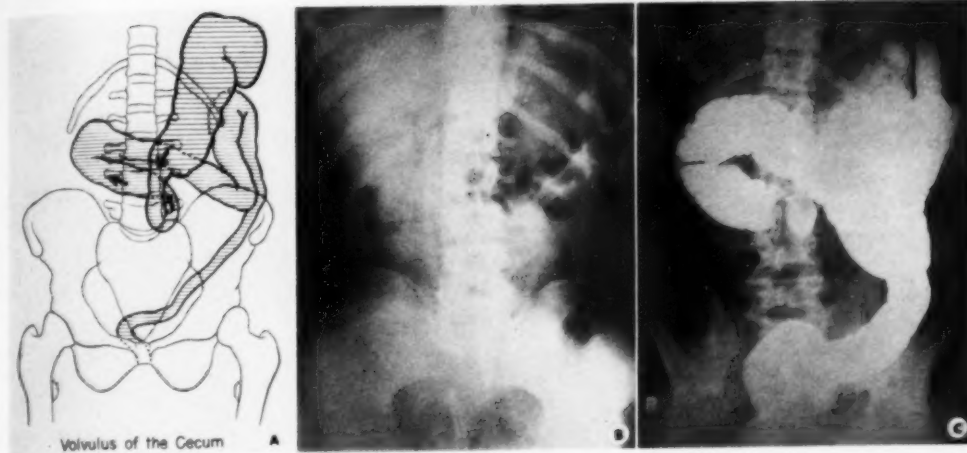


Fig. 9. Case 9.

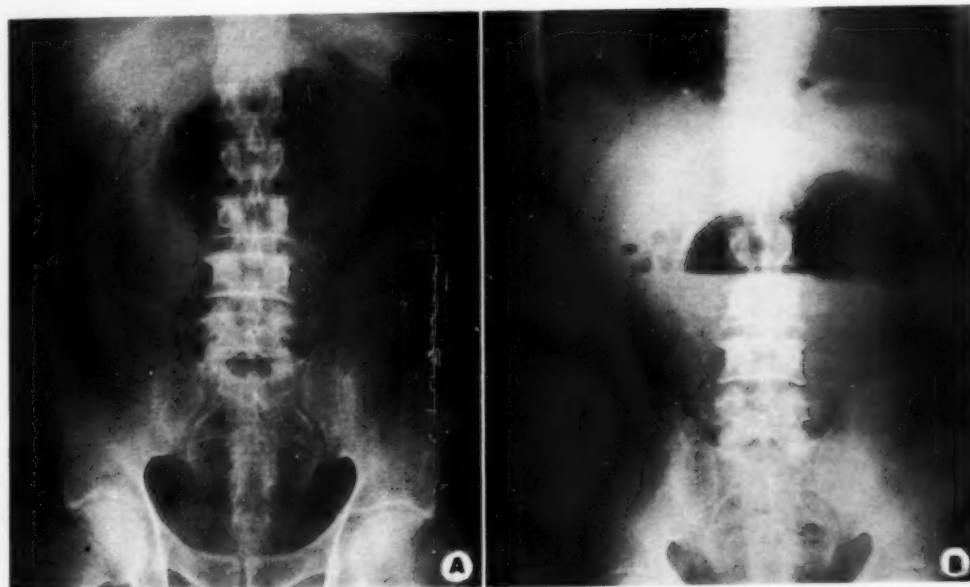


Fig. 10. Case 10.

diaphragmatic leaf rules out a distended stomach; moreover, a definite fluid level is seen in the stomach on the upright study (Fig. 10A and B).

CASE 11: F. H., a 67-year-old white male, was admitted on Jan. 29, 1952, with generalized cramping abdominal pain, distention, and nausea of twenty hours duration. Except for occasional mild episodes of cramping abdominal pain, the past history was inconsequential.

Anteroposterior and upright studies of the abdomen were made at the time of admission, and the patient was immediately taken to the operating room. At surgery a hugely dilated cecum presented in the left upper quadrant, and practically no gas was found in small or large bowel elsewhere. Torsion of 180° was corrected; bands at the mid ascending colon were severed; a cecopexy was done.

Comment: The tremendous gas and fluid distention of the cecum in the left upper

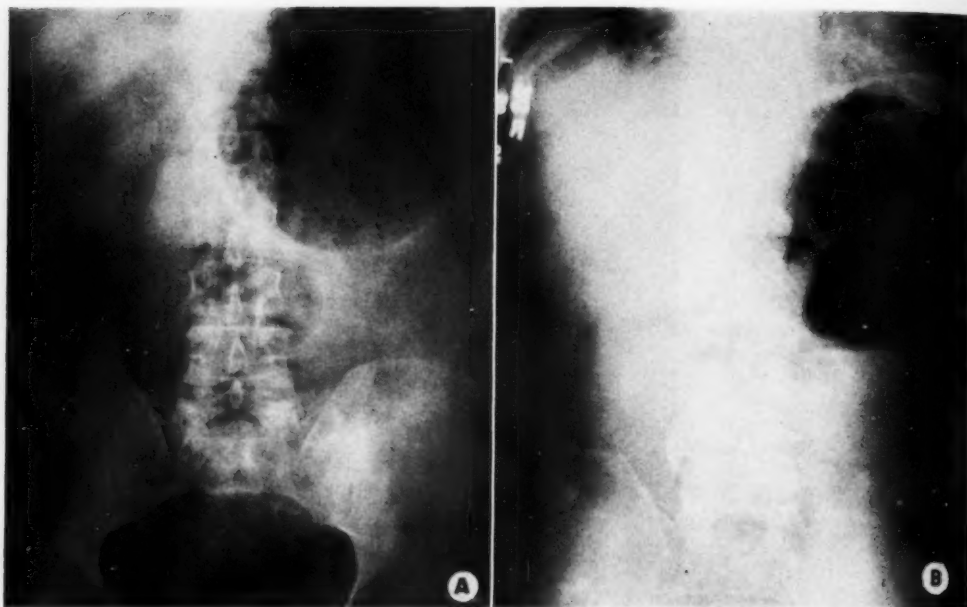


Fig. 11. Case 11.

quadrant and the striking absence of gas elsewhere in the bowel (patent ileocecal valve) are noteworthy. In view of the absence of haustrations and the appearance of the distended viscus, one would certainly consider a dilated stomach. The presence of a small fluid level, however, in intimate relationship to the left diaphragmatic leaf within the shadow of the greatly distended viscus suggests minimal gastric distention. The only logical conclusion is that the distended viscus must be cecum (Fig. 11A and B). In such cases, gastric aspiration or a small barium meal would permit of immediate differentiation.

CASE 12: O. H., a 26-year-old colored female, was admitted on Jan. 21, 1951, on her eighth postpartum day, with severe cramping abdominal pain, distention, and vomiting. Symptoms began three days postpartum and had gradually increased in severity. There had been no bowel movements since the onset.

Scout studies of the abdomen and a barium enema revealed findings which were interpreted as indicating complete colonic obstruction as a result of volvulus.

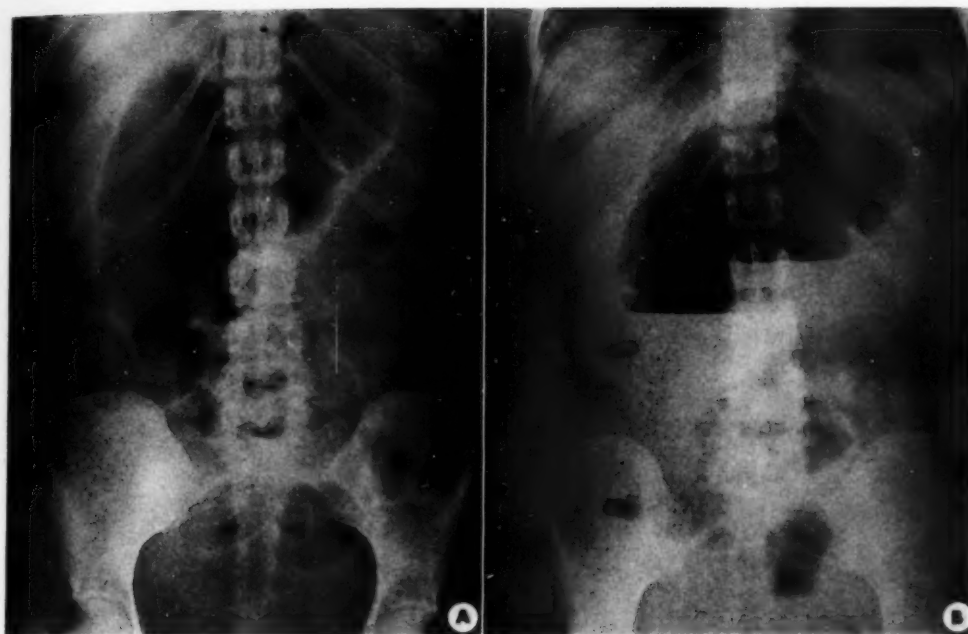
Surgical exploration revealed a gangrenous cecum and ascending colon in the epigastrium and left upper quadrant. The gangrenous bowel was re-

sected and an ileotransverse colostomy performed. The patient was discharged on Feb. 3.

Comment: Note the tremendous gaseous and fluid distention of the right colon which presents in the epigastrium. Haustral markings were maintained in spite of severe distention. The picture resembles an inverted cecum and right colon. The stomach is identified above the right colon in the upright film. The point of torsion is outlined by gas and its position confirmed by contrast studies (Fig. 12A, B, and C).

This case presents several interesting features. Since the point of torsion was outlined in the proximal transverse colon on the barium enema study, we believe this to be a case of non-rotation of the colon complicated by torsion occurring as a postpartum accident.

CASE 13: L. N., an 18-year-old female, was admitted on Dec. 14, 1946, with cramping periumbilical pain, nausea, and vomiting. Physical examination revealed a visible tender mass in the left lower quadrant. On vaginal examination, the uterus was found to be enlarged to the size of an orange, with the cervix soft and bluish in appearance.



Figs. 12A and 12B. Case 12.



Fig. 12C. Case 12.



Fig. 13. Case 13.

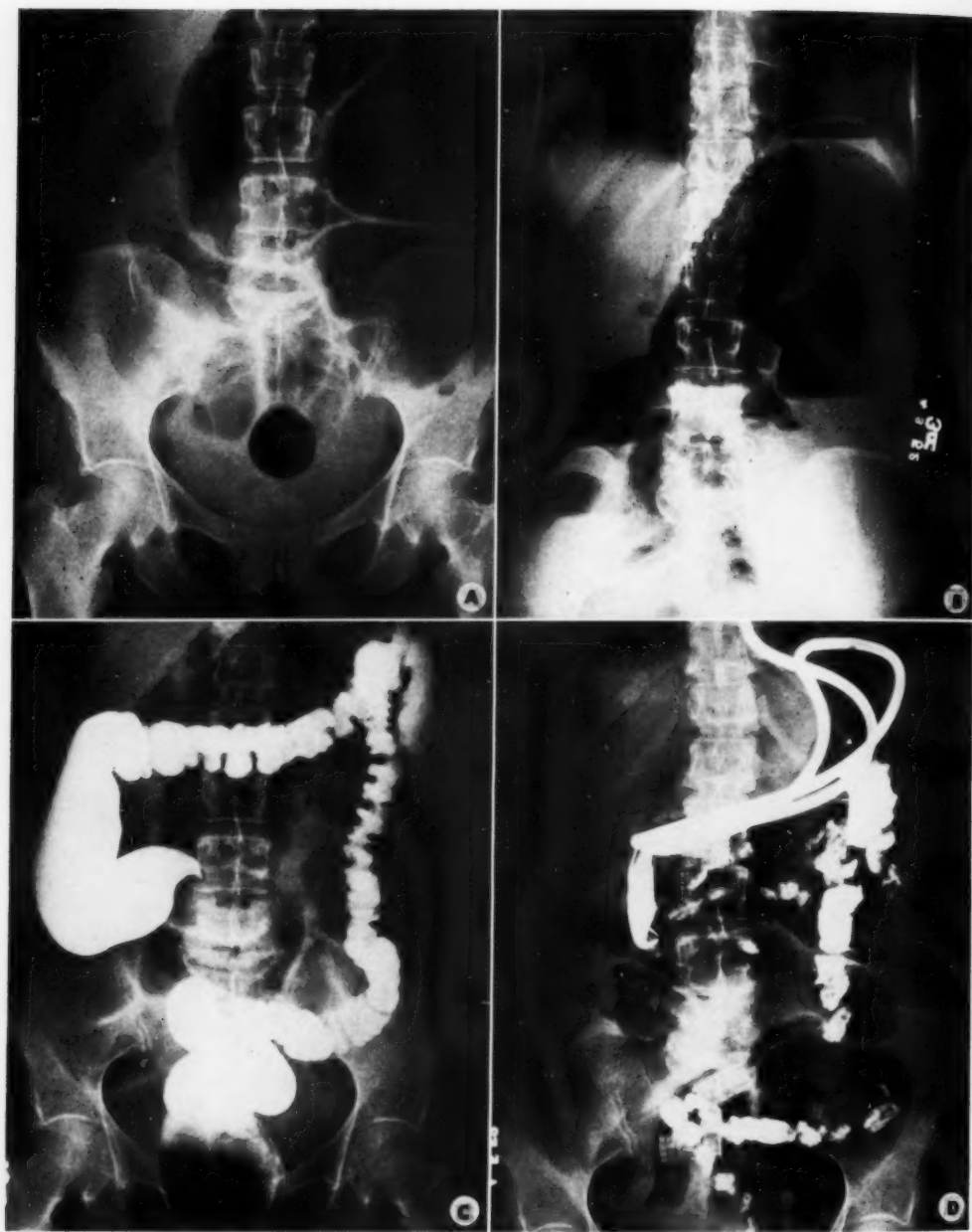


Fig. 14. Case 14.

A scout film of the abdomen was interpreted as indicating volvulus of the sigmoid.

Surgical exploration through a left transverse incision revealed a large distended colonic segment in the left mid abdomen, identified as cecum and ascending colon. Simple detorsion was done, with

no attempt at fixation, because of the marked distention of the involved segment.

Comment: The roentgen appearance of the gas-distended loop of right colon suggests inverted cecum. Other features are

haustrations, mild small bowel distention, and relative absence of gas and fecal matter in the distal colon (Fig. 13).

CASE 14: M. S., a 52-year-old white woman, was admitted on April 2, 1952, with cramping abdominal pain, distention, nausea, vomiting, and constipation lasting four days. Radiological examination revealed excessive distention of a rather large colonic segment occupying most of the left flank and of some ileal loops in the right mid abdomen. Colonic distention was otherwise absent, especially in the right flank and right iliac fossa (Fig. 14A and B). The tentative diagnosis was volvulus of the cecum with faulty anatomic orientation and pronounced displacement; obstruction somewhere in the ascending colon. A contrast study revealed obstruction at the point of torsion overlying the fourth lumbar vertebra (Fig. 14C).

At operation a cecal volvulus of 540° was corrected and abnormal peritoneal attachments of the right hemicolon near the hepatic flexure were freed. Resection of the right hemicolon and ileocolostomy were not considered advisable at this time. The patient recovered gradually.

A postoperative scout study of the abdomen revealed severe distention of a markedly hyperdescended and elongated cecum with the cecal base superimposed upon the left iliac bone and directed superiorly (Fig. 14D).

Comment: A critical analysis of the initial survey films permitted a correct diagnosis, which was confirmed by the contrast study of the colon.

SUMMARY

1. A total of 447 cases of volvulus of the cecum have been reported in the available literature, to which are added 24 new cases, making a total of 471 cases.

2. The roentgenographic picture of cecal volvulus is somewhat variable. However, two main groups are identifiable. (a) A large group of cases, approximately 60 per cent in our series, in which, due to the completeness of the obstruction, the distal colon will be completely or relatively devoid of gas and fecal matter. In this group there is an unusual tendency for the cecum to migrate to an abnormal location, the most common being the left upper quadrant. (b) The second group consists of cases of partial torsion, in which the incompleteness of the obstruction permits passage of gas into distal colonic segments,

the degree of distention being such that the obstruction cannot be accurately localized without a contrast enema.

3. Partial torsion of the right colon with incomplete obstruction should be suspected in all cases in which the radiographic studies demonstrate disproportionate cecal distention. Suspicion of partial torsion may be enhanced by: (a) demonstration of a fluid level in the cecum; (b) demonstration of an apparent discontinuity of the gas pattern in the proximal colon near the hepatic flexure; (c) demonstration of progressive cecal distention on subsequent observations; (d) demonstration of a progressive tendency toward cecal dislocation on progress studies; (e) demonstration of a characteristic obstruction on examination of the colon with a barium enema.

4. The reported incidence of volvulus of the right colon should increase perceptibly if the above criteria are adhered to. Fewer cases should be mislabeled as "severe ileus, cause undetermined," or obstruction secondary to bands or adhesions along the ascending colon.

NOTE: We are deeply grateful to our preceptor, H. A. Jarre, M.D., for his invaluable aid in the preparation of this paper. We are also deeply indebted to Dr. Wm. A. Irwin, Radiologist, Providence Hospital; Dr. I. D. Harris, Radiologist, Wyandotte General Hospital; Dr. V. C. Johnson, Radiologist, Harper Hospital; Dr. E. M. Savignac, Radiologist, Holy Cross Hospital; and Dr. J. Zbikowski, Radiologist, Wayne County General Hospital, whose contributions of cases for study have permitted the analysis of a sufficiently large and varied series to permit a more accurate evaluation of the findings in this condition.

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SUMARIO

Vólvulo del Ciego y del Colon Ascendente

En la literatura accesible, se ha descubierto un total de 447 casos de vólvulo del ciego, a los que se agregan ahora 24 casos, formando un total de 471. Preséntanse sumarios de 14 historias clínicas.

El cuadro roentgenográfico del vólvulo cecal es algo variable, mas pueden identificarse dos grupos principales.

(1) En un grupo numeroso (aproximadamente 60 por ciento de los casos de la serie de los AA.), debido a lo completo de la oclusión, el colon distal estará total o relativamente vacío de gas y materias fecales. En ese grupo, existe una tendencia extraña de parte del ciego a migrar a un sitio anómalo, siendo el más común el hipocondrio izquierdo.

(2) El segundo grupo consta de casos de torsión parcial, en los que la oclusión incompleta deja pasar gas a los segmentos

distales del colon, produciendo tal distensión que no puede localizarse la obstrucción sin la ayuda de una enema de contraste. Debe sospecharse torsión parcial de la porción derecha del colon con oclusión incompleta en todo caso en que los estudios roentgenológicos revelen desproporcionada distensión cecal. Una sospecha de torsión parcial puede ser reforzada por: (a) descubrimiento de líquido en el ciego; (b) descubrimiento de una aparente interrupción del patrón del gas en la porción proximal del colon, cerca de la flexura hepática; (c) descubrimiento de distensión cecal creciente en las observaciones subsiguientes; (d) descubrimiento de una tendencia cada vez más acentuada hacia la dislocación cecal en estudios sucesivos; (e) descubrimiento de una típica obstrucción al examinar con una enema de bario.



Developmental Abnormalities of the Duodenum Producing Obstruction¹

RICHARD F. McCLURE, M.D., and ELMER F. WAHBY, M.D.

THE EMBRYOLOGICAL development of the duodenum and its peritoneal membranes is so complicated that obstructing anomalies are sometimes present after birth. Although such congenital duodenal obstructions are uncommon, their mortality rate is so high that they assume a most important role among diseases of infants and children (26).

Congenital obstructing lesions of the duodenum may be classified as follows (9):

- I. Intrinsic
 - A. Atresia
 - B. Stenosis
- II. Extrinsic
 - A. Persistent cholecystoduodenocolic membrane
 - B. Abnormal fixation of the duodenum permitting volvulus
 - C. Annular pancreas or aberrant pancreatic tissue
 - D. Vascular anomalies
 - E. Prenatal development of mesenteric cysts
 - F. Cysts of the liver and pancreas

In the four-week embryo the gut exists as a simple hollow tube suspended between a long dorsal mesentery and a shorter ventral mesogastrium. The duodenal segment of the primitive gut rapidly lengthens into a distinct intestinal loop, which rotates counterclockwise about the superior mesenteric artery. The mesoduodenum is laid against the dorsal body wall and is obliterated, fixing the duodenum in its permanent position. The pancreas, lying within the leaves of the mesoduodenum, becomes a retroperitoneal organ. The liver, growing rapidly between the layers of the ventral mesogastrium, reduces it to a structure recognized as the hepatogastric ligament, which fades out in the peritoneum of the anterior duodenal wall.

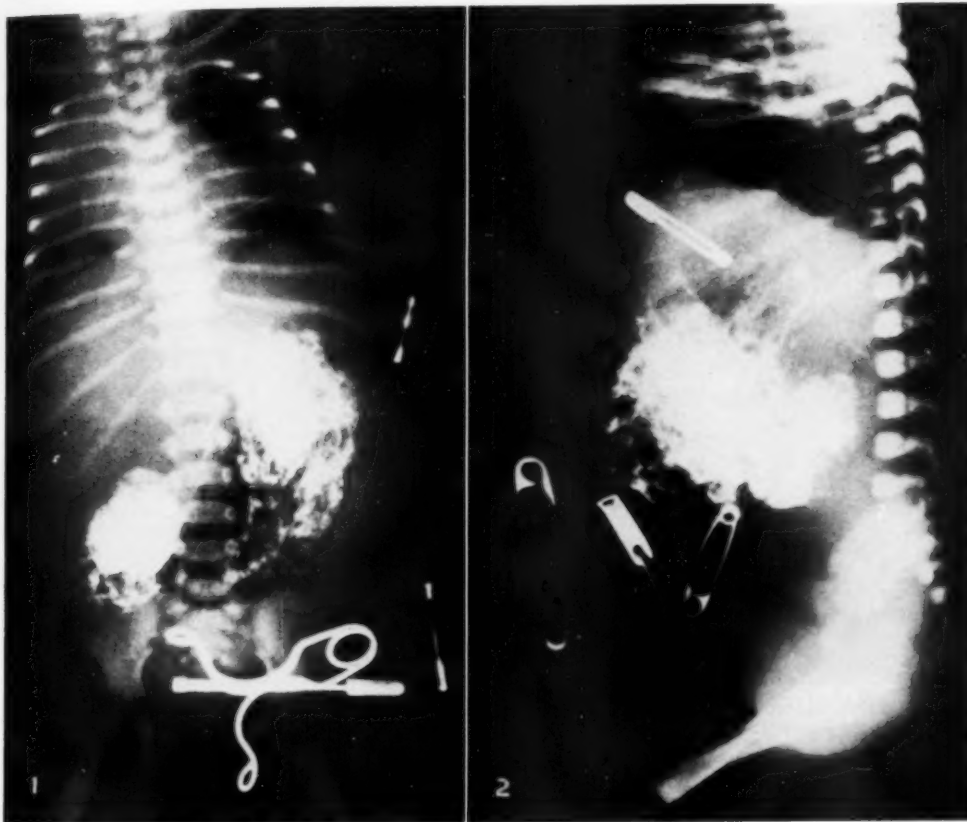
Between the sixth and tenth weeks of fetal life remarkable changes take place in

the lumen of the duodenum. The mucosal epithelium proliferates and occludes the canal. Soon vacuoles appear in this plug of tissue, and these rapidly coalesce until the patency of the duodenum is re-established.

Congenital anomalies of the duodenum do not develop as such. They exist because, at one stage or another in its embryology, the normal development is delayed or arrested (23). If the appearance of the ventral pancreatic rudiment is delayed, or if the left wall of the duodenum fails to grow more rapidly than the right wall, the ventral pancreatic rudiment is not turned dorsad, and an annular pancreas develops. Areas of aberrant pancreatic tissue are simply the result of multiple pancreatic primordia. Atresia exists when the plug of duodenal epithelium fails to recanalize. Incomplete coalescence of the vacuoles produces one or more diaphragms in the lumen of the duodenum. A duodenal stenosis is present when recanalization is established but epithelial resorption is not completed. When obliteration of the dorsal mesoduodenum fails, the freely swinging duodenum may twist on itself and produce a volvulus. When obliteration occurs but the mesentery of the small bowel does not shorten sufficiently, the superior mesenteric artery may be weighed down over the duodenum and constrict it. Finally, when the ventral mesogastrium is not obliterated and becomes attached secondarily to the colon, we recognize the existence of a cholecystoduodenocolic membrane.

Many writers have called attention to the presence of congenital obstructing lesions of the duodenum (6-9, 12, 14, 19, 24, 26). The problems of atresia and stenosis have been their chief concern. Briefly, the clinical picture is one of intes-

¹ From The Henry Ford Hospital, Detroit, Mich. Presented at The Thirty-eighth Annual Meeting of the Radiological Society of North America, Cincinnati, Ohio, Dec. 7-12, 1952.



Figs. 1 and 2. Case I: An anteroposterior view of the abdomen (Fig. 1) shows barium and gas in the stomach with no evidence of gas in the small bowel or colon. The lateral view (Fig. 2) again shows barium and gas confined to the stomach and duodenal bulb.

tinal obstruction wherein bile-stained vomitus points to a site below the ampulla of Vater, bile-free vomitus indicates obstruction above the ampulla, and bile-free vomitus plus bile-free stools suggests complete duodenal atresia (12). It is not our purpose to restate the significance of these atresias and stenoses and the diagnostic problems involved. They are illustrated by the following case.

CASE I (Figs. 1 and 2): A newborn female having mongoloid facies vomited brownish material frequently. Roentgen examination showed that barium did not pass beyond the ampulla of Vater. The child died after three days. Autopsy revealed a dilated pylorus and a segment of atresia 8 mm. long proximal to the ampulla of Vater.

It should be emphasized here that we do

not recommend that barium be used in a newborn infant with intestinal obstruction. The diagnosis can and should be made from a plain film of the abdomen without the introduction of a radiopaque medium (17, 24).

Not all congenital obstructions of the duodenal loop are simple stenoses or atresias. The most common condition in our classification of extrinsic causes is the cholecystoduodenocolic membrane, often referred to as a "duodenal band" (2). These bands may, through extrinsic pressure, produce obstruction in infants and adults alike. Bryant (2) in an extensive study of these structures in 1922 found bands involving the duodenum in 47.9 per cent of males and in 53 per cent of females

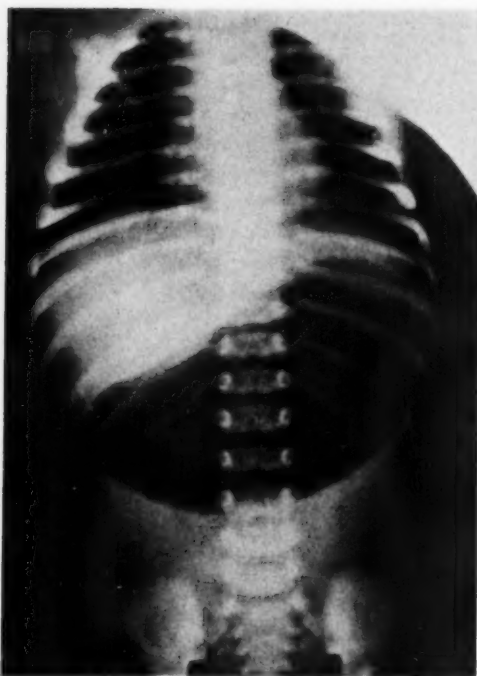


Fig. 3. Case II: Anteroposterior film showing gas confined to the stomach; no gas in the small bowel or colon.

of all ages. He observed that the bands most commonly encountered in the adult are the same as those most frequently found in fetuses. These bands are, therefore, primarily congenital in origin.

Harris (10), Homans (14), and Hill (13) have reported cases in which cholecystoduodenocolic bands produced symptoms severe enough to warrant surgical exploration. The chief symptoms are attacks of epigastric pain and intermittent indigestion, often dating from childhood. Fullness after meals and belching two to three hours after eating are common complaints. Vomiting may afford relief. The symptoms mimic closely those of duodenal ulcer, gallbladder disease, and gastrointestinal cancer.

The deformities produced by duodenal bands on the roentgenogram are (a) constriction of the anterosuperior surface of the duodenal bulb; (b) a feathery irregularity of one surface of the bulb, with the

opposing surface appearing smooth; (c) irregularity of the pyloric antrum and sphincter; (d) high fixation of the duodenal bulb associated with a dilated ptotic stomach (5, 15, 22). These deformities are more obvious in the erect or prone position. When the patient lies horizontally in

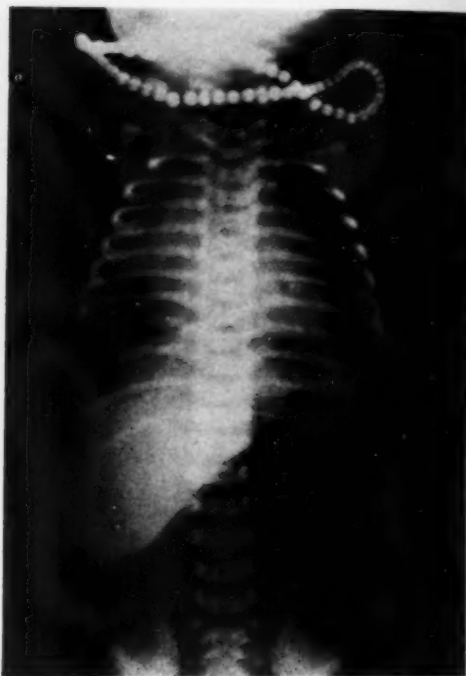
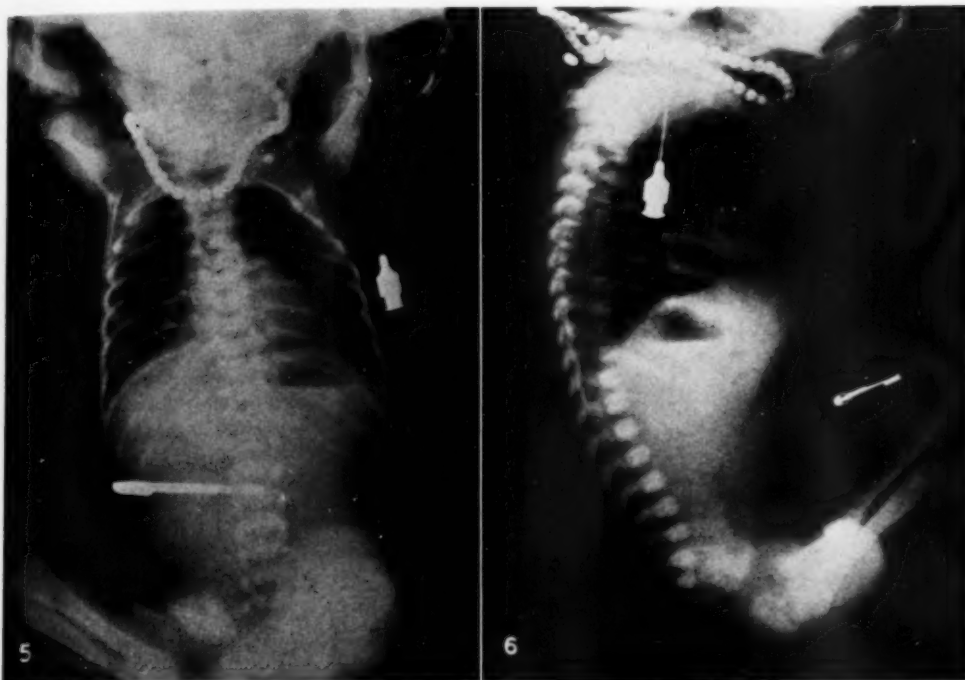


Fig. 4. Case III: Anteroposterior film showing gas confined to the stomach.

the right anterior oblique position, they may disappear.

At the Henry Ford Hospital we have found 8 proved cases of duodenal bands causing severe symptoms of obstruction, 4 of which will be briefly summarized. These congenital membranes are quite often discovered during exploration of the gallbladder area. Cole (5) has aptly described their gross appearance as "veils." Actually they may exist either as a thin band or as many fine strings of tissue forming a web which overlies the duodenum.

CASE II (Fig. 3): A white male infant began to vomit bile-stained material on the eighth day of life. The abdomen was distended. Roentgen examination showed air in the stomach but not in



Figs. 5 and 6. Case IV: Both anteroposterior (Fig. 5) and lateral films (Fig. 6) show gas and fluid in the stomach: no gas in the small bowel or colon.

the small bowel. Lipiodol administered orally did not pass beyond the second portion of the duodenum. At operation a band of tissue was found stretched tightly across the duodenum from the gallbladder to the colon, and another at the duodenojejunal junction. The cecum lay in the left side of the pelvis. All symptoms were relieved after severance of the bands.

CASE III (Fig. 4): A premature female infant vomited all feedings. Roentgen examination showed air in the stomach but not in the small bowel. The child died after four days. Autopsy revealed dilatation of the stomach and first two segments of the duodenum. A thick band of tissue compressed the third portion of the duodenum. The intestinal tract was otherwise normal.

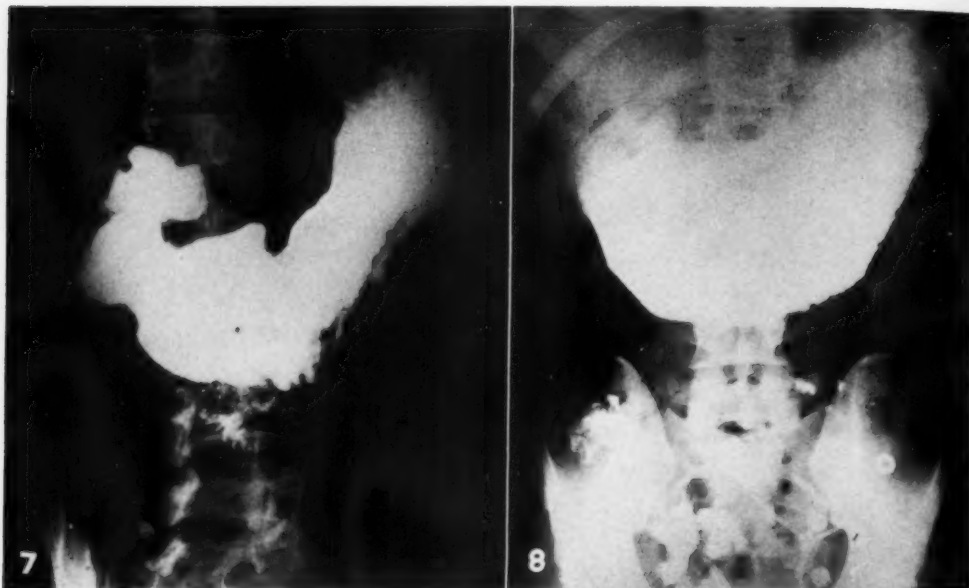
CASE IV (Figs. 5 and 6): A newborn white male vomited all feedings. Roentgen examination showed air and fluid in the stomach but no air in the intestinal tract. Death occurred on the fifth day. Autopsy revealed incomplete expansion of the lungs, dilatation of the proximal two-thirds of the duodenum and a band constricting the fourth portion of the duodenum.

CASE V (Figs. 7-10): A 23-year-old white male complained of postprandial vomiting for seven months, and frequent nausea. On admis-

sion to the hospital he retained only liquid foods. Roentgen examination showed deformity of the duodenal bulb without a visible crater, and almost complete retention of stomach contents at six hours. At surgery the duodenal bulb was found to be normal. A band of tissue was stretched tightly across the second portion of the duodenum from the gallbladder to the transverse colon. A partial gastrectomy was performed after severance of the band because of severe gastric dilatation and redundancy associated with gastritis and duodenitis.

Mahoney (18), in 1941, reported 18 cases in which the presence of duodenal bands was proved surgically. In 13 of these complete relief from symptoms followed operative release of the bands. Three patients improved, and in 2 there was no change in symptoms.

In conclusion, then, duodenal obstruction in a newborn infant may be due to atresia or stenosis. A more common anomaly than either of these is the cholecystoduodenocolic membrane which compresses the duodenum. It can exert sufficient pressure to produce obstruction.



Figs. 7 and 8. Case V: An oblique film of the stomach (Fig. 7) shows deformity of the duodenal bulb suggestive of an ulcer scar. Only a very small amount of barium has left the stomach. A six-hour film (Fig. 8) shows almost complete retention of barium in the stomach.



Fig. 9. Case V: Artist's sketch made at operation, showing the duodenal band extending from the gall-bladder across the apex of the duodenal bulb to the colon.

Although present at birth, the duodenal band may produce only vague symptoms until adulthood, at which time obstructive phenomena may appear. On the roentgenogram such a band may resemble a duodenal ulcer deformity. Radiologists should not forget the relatively common occurrence of the cholecystoduodenocolic membrane and that it may be the cause of duodenal deformity and obstruction in a patient of any age.

SUMMARY

1. Congenital anomalies of the duodenum have their origin in delay or arrest of development at some stage in the embryology of the duodenum.
2. The common congenital obstructing lesions are atresia, stenosis, and cholecystoduodenocolic membranes.
3. The roentgenographic deformity produced by duodenal bands has been described.
4. A congenital duodenal band is to be considered in the differential diagnosis of duodenal bulb deformity.



Fig. 10. Case V: Artist's sketch showing the severed duodenal band. The duodenum clearly bears on its surface the impression of this tight band.

Note: This case is presented through the courtesy of Drs. R. J. Priest, L. J. Gregory, and J. Barron of The Henry Ford Hospital.

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SUMARIO

Vicios de Desarrollo del Duodeno Produciendo Oclusión

Las anomalías congénitas del duodeno tienen su origen en la tardanza o cese del desarrollo en algún período de la embriología duodenal. Los estados oclusivos

más comunes son atresia y membranas colecistoduodenocólicas.

Las deformidades producidas por bandas o membranas duodenales, observadas roent-

genológicamente, son: (a) constricción de la cara anterosuperior del bulbo o capuchón duodenal; (b) irregularidad plumosa de una cara del bulbo, mientras que la opuesta parece lisa; (c) irregularidad del antro y del esfínter pilórico; (d) fijación alta del bulbo duodenal, asociada a dilatación y ptosis del estómago. Esas deformidades son más manifiestas cuando el enfermo se halla erguido o en decúbito

prono. El cuadro puede semejar la deformidad de una úlcera duodenal.

Descríbense sucintamente un caso de atresia simple y 4 casos de bandas duodenales (3 en lactantes y 1 en un adulto).

Los radiólogos no deben olvidar la ocurrencia relativamente común de bandas o membranas colecistoduodenocólicas, que pueden ser una causa de deformidad duodenal a cualquiera edad.

DISCUSSION

Benjamin Felson, M.D. (Cincinnati, Ohio): I would like to congratulate the authors on an interesting and instructive paper. As I read it, a number of thoughts passed through my mind; these form the basis of my discussion.

In the first place, are we missing these duodenal bands in the adult patient? They certainly are common enough at operation and at autopsy: 40 per cent of all individuals are said to have such cholecystoduodenocolic bands or membranes. Perhaps they are simply normal variants. In the older literature these anomalies were commonly thought to be symptomatic, and the roentgen findings diagnostic. It is my personal belief that they rarely produce symptoms and that the roentgen diagnosis is quite difficult, except perhaps for the cases with partial obstruction. To me, these bands appear more important as a cause of deformity of the bulb or antrum, which may be difficult or impossible to distinguish from duodenal ulcer or gastric carcinoma, as the authors have pointed out. Perhaps some of the cases of so-called gallbladder adhesions which have caused deformity of the duodenal bulb or antrum are, in reality, cholecystoduodenocolic membranes, which the surgeon mistakes for gallbladder adhesions.

Secondly, I do not believe that the exact diagnosis of the type of obstruction can often be made from the plain film. The preoperative differential diagnosis between atresia, stenosis, duodenal band, etc., is not, however, important. Partial obstruction in the infant may not infrequently be associated with a normal film of the abdomen. In such cases I see no harm in administering barium by means of a tube, under fluoroscopic control (sucking out the excess of barium afterward), or using Lipiodol, to establish simply the diagnosis of obstruction or partial obstruction. Certainly, we would not advise delay in operation where the obstruction is evi-

dent on the plain film, in order to find the specific cause. The treatment is surgical, and the sooner the better.

Thirdly, I noted that malrotation of the colon was present in Case II. This is common in all congenital obstructions, and occasionally, when the plain film of the abdomen is not diagnostic of obstruction, we may raise our index of suspicion by demonstrating malrotation with the barium enema.

Finally, the infant with duodenal atresia had mongoloid features. Bodian and his associates (Brit. M. J. 1: 77, Jan. 12, 1952) recently collected 32 cases of duodenal atresia or severe stenosis from the literature and their own experience, and found that one-third of these patients were mongols. Dr. William Duffey of our Department reviewed the records of 8 infants with duodenal atresia or stenosis at Children's Hospital. Two of these 8 were mongols. I feel reasonably certain that mongolism is even more common than these figures indicate, since it is well known that mongoloid features are frequently missed during the newborn period.

Dr. McClure (closing): I will just say that I don't want anyone to have the impression that we diagnose duodenal bands and then tell the surgeon to operate, because that is pure foolishness. We do want to make this important point: that in cases that come up for examination and re-examination again and again, with a deformed duodenal bulb and a clinical history that doesn't fit too well, one of the things that should enter our minds is the possibility of a band. In the absence of real obstructing symptoms, it is not a good thing to operate. But a band is one of the things that, at least for our own intellectual curiosity, it is interesting to know about and to consider in the differential diagnosis.

The Prepyloric Suspect Lesion¹

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THERE IS A difference of opinion among radiologists as to what constitutes a satisfactory x-ray report. Some make it a practice to describe in detail the physical routine used in completing the roentgen examination and give a long description of the findings. The other extreme is a report limited to a diagnosis, while in between are all of the variations which could be anticipated.

It is quite possible that either extreme could be useful under certain circumstances, though special emphasis should be given to the fact that the referring physician has sent the patient for a consultation and is not interested in the way in which the x-ray tools are used or in the manner in which the radiologist reaches an opinion. He is interested in a diagnosis, or a differential opinion if a diagnosis cannot be given, and should appreciate greatly any help as to the accepted method or manner of handling the case if it is a difficult or complicated one and comes within a grouping in which the radiologist is particularly skilled or has special knowledge or interest. Under these circumstances, the consultation is most rewarding to the referring physician, who is thereby able to expedite the necessary procedures to establish a diagnosis and hasten the patient's recovery.

This type of practice of radiology finds one of its greatest opportunities in studies of the intestinal tract, and particularly in dealing with prepyloric suspect lesions. The accuracy of roentgen diagnosis of gastrointestinal tract lesions is so well known and so widely accepted that the radiologist is usually given the opportunity, early or late, to examine most patients who have symptoms suggesting digestive disease. To be effective in its results the

x-ray study requires great skill, and the lesion in the stomach must be of sufficient magnitude to produce recognizable abnormalities on the screen and films of diagnostic significance.

The source of patients with gastrointestinal-tract symptoms seen by the radiologist is significant, in that a high percentage are referred by men who are not gastroenterologic internists or physicians especially skilled in the treatment of digestive disease. When the x-ray diagnosis is a prepyloric suspect lesion, the responsibility of the radiologist increases greatly because of the necessity of emphasizing the potential seriousness of the condition to the general physician and suggesting an appropriate procedural program and follow-up regime.

As used in this paper, the term prepyloric suspect lesion, *i.e.*, carcinoma suspect, designates a persistent deformity in the contour or an aberration in the mucosal pattern of this portion of the stomach of such character as to make an unqualified x-ray diagnosis impossible. It would thus include both additive (ulcer) and subtractive (infiltrative) lesions, and a combination of the two, as well as extragastric deforming processes.

One is probably justified in the opinion that the medical campaign for earlier diagnosis has had some desirable effect upon the general public. Significant symptoms of serious disease of the intestinal tract have been given wide publicity, and patients have been urged to consult their doctors early when changes in normal digestive-tract habits are noticed. Too many make a self diagnosis of dietary indiscretion and indulge in self medication and a self-imposed diet. This often lessens the distress for weeks and even months, and

¹ X-Ray Department, Fitzgerald-Mercy Hospital, Darby, Penna. Presented at the Thirty-eighth Annual Meeting of the Radiological Society of North America, Cincinnati, Ohio, Dec. 7-12, 1952.

it is not until it is re-established or increases in severity in spite of self treatment that the physician is consulted. Frequently, when obtaining a history from a patient, one learns that the family doctor has been treating dyspepsia for some time with dietary regulations and medicine, without an exact knowledge of the type of disease present.

Wangensteen (1) has recently given emphasis to "the silent interval" in gastric cancer, suggesting that the disease may be present for six to twenty months before symptoms occur. Continued education of both the public and the physician must be carried out, stressing the importance of persistent gastrointestinal symptoms and the need of prompt and accurate identification and localization of the disease.

Berkson *et al.* (2) report a five-year salvage of 32 per cent of cases of gastric carcinoma when the lesion is resectable. When there are no metastases at the time of gastric resection, the five-year survival percentage rises to 50. It is not unlikely that even better results can be obtained if patients with suspect lesions are sent to the surgeon earlier, a responsibility which must be shared by the patient and the general practitioner alike, and a challenge to the radiologist to give as much help and information as is pertinent with his report of the x-ray examination.

When diagnostic x-ray studies reveal prepyloric disease, what part should the radiologist play in the procedural program arising from the discovery of this type of lesion? His role would seem to be governed primarily by the origin of the referral. If one is fortunate enough to be associated with gastroenterologic internists or physicians trained in the problem of treating disease of the gastrointestinal tract, a description of the size and location of the lesion, its roentgen characteristics, and its relationship to gastric motor function may suffice. Further studies relating to gastric secretory function and occult blood determinations would be correlated with the age of the patient and the duration and character of the symptoms. All

would be evaluated, and a choice between medical and surgical treatment would be made.

When, on the other hand, the patient is referred by a physician in general practice, the radiologist's problem assumes different proportions and should become one of giving as much information and aid to the family doctor as is available. With such a diagnosis, the gravity of a lesion in this portion of the stomach must be emphasized, and prompt complementary clinical and laboratory studies must be obtained and evaluated before a final opinion and conclusion can be given. It might be helpful at this time to review briefly some of our present knowledge regarding the usual clinical and laboratory findings in prepyloric suspect lesions.

AGE AND SEX

In a large series (3) of gastric resections for proved gastric cancer, the mean age was fifty-five years, although *1 per cent were in the decade twenty-to-twenty-nine years, and about 8 per cent were under forty.* There were three and a half times as many men as women. There does not seem to be any relationship between age or sex and the rate of growth, type, or location of the malignant process.

SYMPTOMS

Patients with a high threshold for gastric dysfunction may show a surprising degree of involvement in the stomach at the time of the x-ray examination, and yet have very little in the way of subjective findings. Again, a small ulcerative lesion near the pylorus may produce much muscle spasm with its attending discomfort. The presenting symptoms vary from patient to patient and are usually due to some aberration of gastric motility or to peritoneal irritation. A frequent early complaint may be a sense of epigastric fullness with distention, as if a heavy meal had been taken, though the patient may have experienced an early satiety and perhaps some nausea. This may be interpreted as due to dietary indiscretion, and restriction

of the type and quantity of food may afford temporary relief.

Some patients will complain of an empty stomach sensation with a hunger-pain type of distress, suggestive of ulcer. The pain distribution may be characteristic, and relief is frequently obtained from food or antacids. This is a significant finding, for Walters' (3) report showed that more than 80 per cent of a large series of patients undergoing gastric resection for verified cancer experienced temporary relief of symptoms when placed on a medical ulcer regime, suggesting that little diagnostic credence can be given to symptomatic relief alone for differentiating between benign and malignant prepyloric ulcerative processes.

Perhaps as many as half of all prepyloric suspect lesions give ulcer-like symptoms at some time (4). Occasionally, there may be a curious sudden change from the ulcer-like chain of events to a sense of gaseous fullness without pain, but with early satiety and nausea, or some other symptom.

When the degree of ulceration is sufficient to erode a blood vessel, hemorrhage may occur, and bleeding is not uncommon in patients who present the ulcer type of complaint. The degree of vascular erosion and the caliber of the vessel involved determine whether the hemorrhage is gross or is occult. Persistent occult bleeding should remind one of the possibility of gastric cancer, for perhaps 50 per cent of patients with malignant disease will show occult blood (4).

Duration of symptoms may be helpful in evaluating prepyloric lesions. Recent onset usually favors a malignant growth. In some cases, however, with a malignant prepyloric lesion, the duration of gastric symptoms may extend over a period of years, suggesting the possibility of some associated disease as a contributing factor. This adds to the burden of evaluating symptoms and increases the difficulties encountered when too much weight is placed upon duration and type of complaints. When a mass is the presenting symptom, or when pyloric obstruction with marked

weight loss is a prominent feature, the usual signs of extensive disease are present and the diagnosis is not difficult.

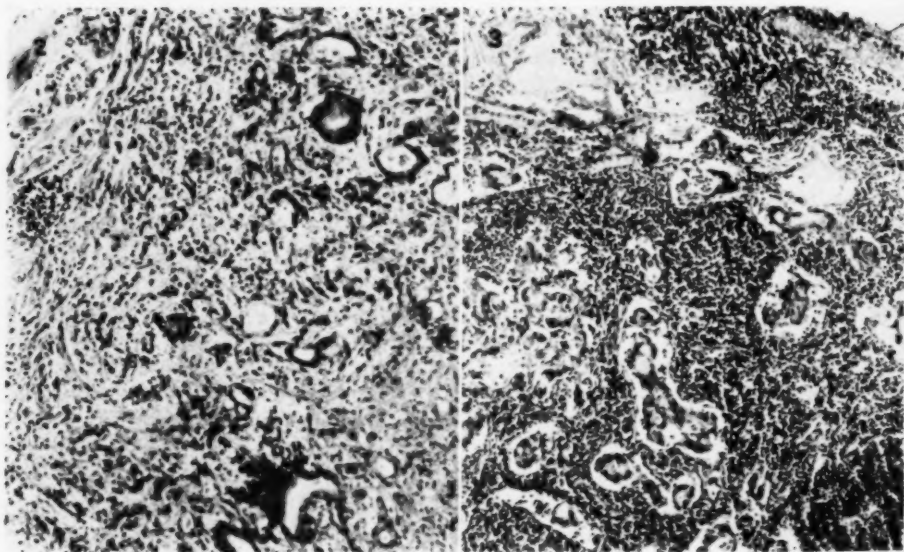
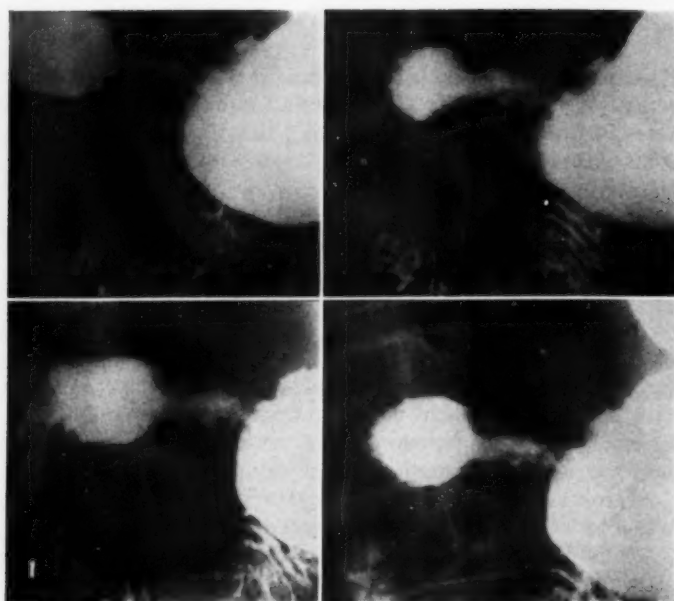
GASTRIC ACIDITY

Hypochlorhydria or achlorhydria is the common laboratory finding in malignant prepyloric lesions, occurring in about 65 per cent of the cases (4); yet the corollary must be emphasized, namely, that 35 per cent have no significant change in gastric secretion or gastric acidity. Eusterman (5) reported free acid in 50 per cent of cases in which resection was done and in 80 per cent of histologically verified gastric cancers. The quantity of secretion and degree of acidity were frequently equal to findings in benign gastric ulcer. This type of laboratory procedure is contributory, but its importance should be evaluated in terms of the total diagnostic problem rather than as an isolated factor.

X-RAY FINDINGS

There is no single sign or combination of x-ray findings which will indicate with certainty whether a prepyloric lesion is malignant or benign. Gray (6) states that 9 per cent of a histologically verified group of gastric cancers failed to show any feature on x-ray examination which could be interpreted as indicative of malignancy. It is safest then to conclude that any prepyloric ulcer or deformity is actually or potentially malignant until proved otherwise.

The roentgenologic data for the prepyloric lesions forming the subject of this paper, while suspicious of malignancy, are such that an unqualified diagnosis cannot be made. There may be an x-ray picture in which ulceration is prominent and the problem is that of benign or malignant ulceration or ulcerating carcinoma, or the evidence may be that of infiltration, in which case tumor is suggested. Not infrequently the x-ray studies may show evidence of both ulceration and infiltration, which is, of course, very suggestive of cancer, but again the findings are not positive enough to allow more than a suspicion as to benignancy or malignancy.



Figs. 1-3. Case I. Male aged 68. Example of long patient delay with self treatment plus inability to make accurate diagnosis until lymph node microscopy.

History: Burning indigestion for more than a year, with quantitative and qualitative food relationship. No satiety but discomfort after eating, for which the patient was taking large doses of alkalis and practising a severe self-imposed diet. Weight loss of 20 pounds.

Laboratory Studies: Essentially normal.

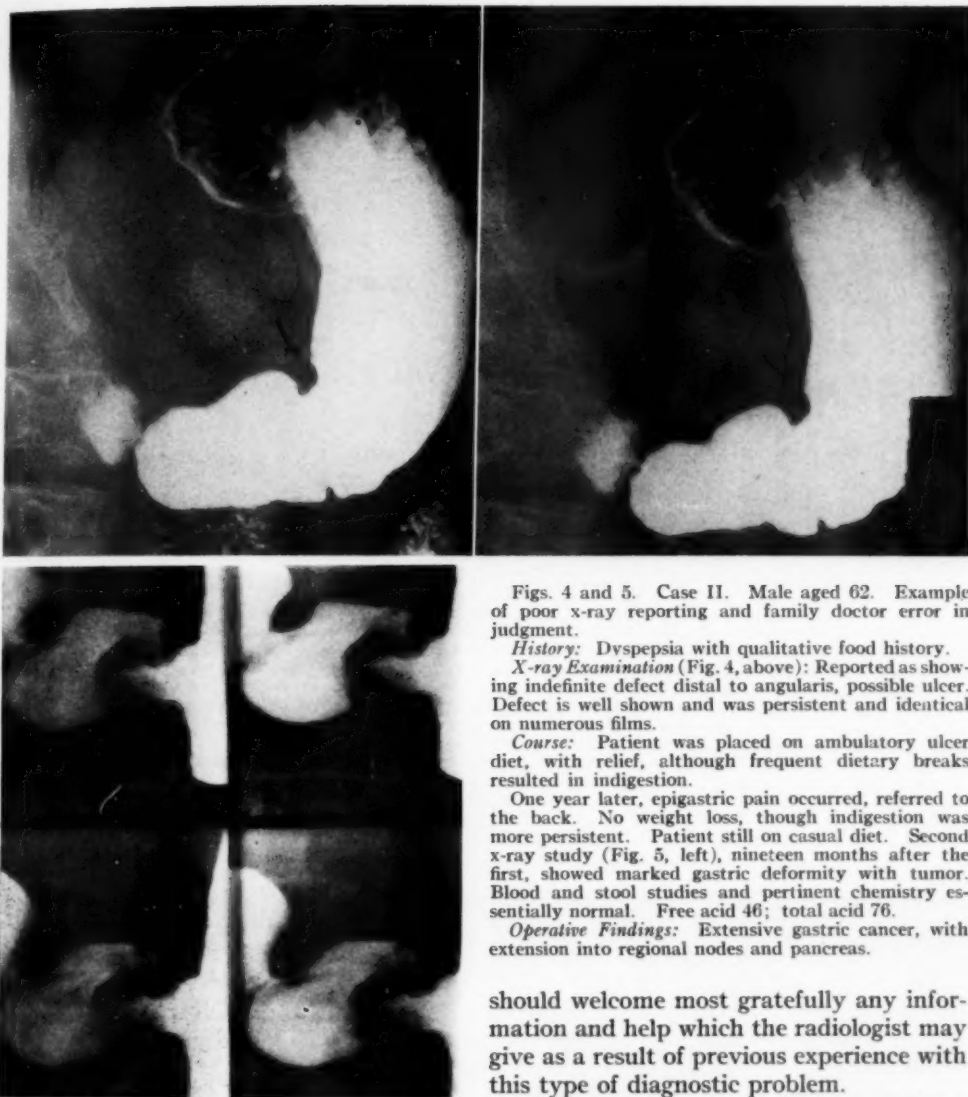
X-ray Examination (Fig. 1): Prepyloric ulcer on lesser curvature, with nothing to suggest malignancy; marked antral deformity which could be due to spasm or cancer. No mass. Tenderness on pressure over antrum.

Operation: Ulcer on prepyloric lesser curvature, thought to be benign, plus antral gastritis. One lymph node approximately 0.5 cm. in diameter found on lesser curvature of stomach. Partial gastrectomy.

Microscopic section through gastric ulcer (Fig. 2) indeterminate. Several pathologists suggested the possibility of cancer but were unwilling to make a conclusive diagnosis.

Section through the one lymph node found at operation (Fig. 3) reveals unquestionable gastric cancer.

This case illustrates the futility of any attempt to make an accurate diagnosis of benignancy or malignancy of an ulcer on the basis of x-ray studies.



Figs. 4 and 5. Case II. Male aged 62. Example of poor x-ray reporting and family doctor error in judgment.

History: Dyspepsia with qualitative food history.

X-ray Examination (Fig. 4, above): Reported as showing indefinite defect distal to angularis, possible ulcer. Defect is well shown and was persistent and identical on numerous films.

Course: Patient was placed on ambulatory ulcer diet, with relief, although frequent dietary breaks resulted in indigestion.

One year later, epigastric pain occurred, referred to the back. No weight loss, though indigestion was more persistent. Patient still on casual diet. Second x-ray study (Fig. 5, left), nineteen months after the first, showed marked gastric deformity with tumor. Blood and stool studies and pertinent chemistry essentially normal. Free acid 46; total acid 76.

Operative Findings: Extensive gastric cancer, with extension into regional nodes and pancreas.

Holmes and Hampton (7) have pointed out the greater tendency of lesions in the prepyloric area and greater curvature of the stomach to malignancy, and Kiernan and Larson (8) have confirmed this, stating that 40 per cent of lesions in the prepyloric region and 96 per cent of those on the greater curvature are malignant.

Statistics such as these should have a profound influence upon the type of x-ray report to be sent to the family doctor, who

should welcome most gratefully any information and help which the radiologist may give as a result of previous experience with this type of diagnostic problem.

This paper reports an experience with a group of prepyloric suspect lesions observed in the general practice of radiology and includes case histories and films illustrative of the problems of diagnosis usually associated with this type of gastrointestinal disease. In addition, an attempt will be made to suggest a procedural routine, with the hope of helping the family physician in establishing a diagnosis, with aid when medical treatment is elected and some pertinent factors to consider when

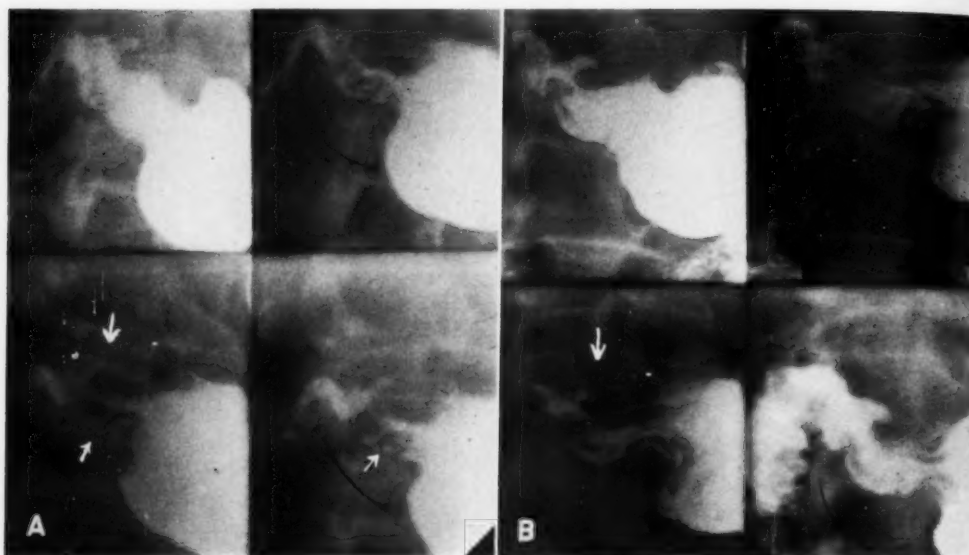


Fig. 6. Case III. Male aged 59. Example of an error on the part of the family doctor in not obtaining earlier x-ray examination.

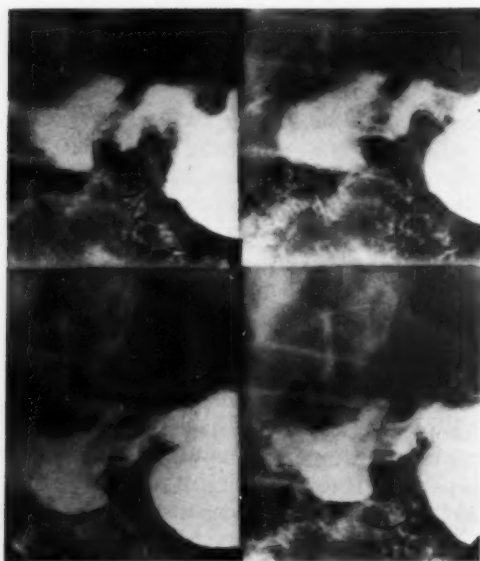
History: Many years of seasonal indigestion with both quantitative and qualitative food history. Much nausea but no vomiting or bleeding. During past year, severe burning epigastric pain following all foods; much nocturnal pain. Recent weight loss and early satiety.

Laboratory Studies: Not helpful.

X-ray Examination (A): Prepyloric defect with induration and mucosal aberration suggesting cancer, plus an active duodenal ulcer. Because of severe pain, the prepyloric mass was considered to be inflammatory and medical management of ulcer was recommended.

Repeat x-ray examination (B), three weeks later, after bed rest and ulcer treatment, showed no significant change. Patient was clinically worse, with increased pain and weight loss.

Operative Findings: Active duodenal ulcer with extensive gastric cancer and metastasis to lymph nodes and liver.



the decision lies between medical therapy and surgical intervention.

PROCEDURAL ROUTINE

When the x-ray examination of the stomach reveals the presence of a prepyloric

Fig. 7. Case IV. Male aged 66. Representative of an x-ray diagnostic problem.

History: Epigastric pain, nausea, and vomiting, seasonal in character and of long duration. Food and alkali relief. Symptoms worse during past six weeks, with much nocturnal back pain. Weight loss of 22 pounds. Tarry stools.

X-ray Examination: Marked gastric deformity in the prepyloric area, with large ulcer on the greater curvature associated with an epigastric mass. *Diagnosis:* Carcinoma of stomach with ulcer.

Laboratory Studies: Moderate anemia. Total acid 10; free acid 0. Chemistry essentially normal.

Operative Findings: Large prepyloric mass with many enlarged nodes. Surgical diagnosis was ulcerating carcinoma with metastasis. Posterior gastroenterostomy with biopsy.

Pathological Diagnosis: Benign gastric ulcer.

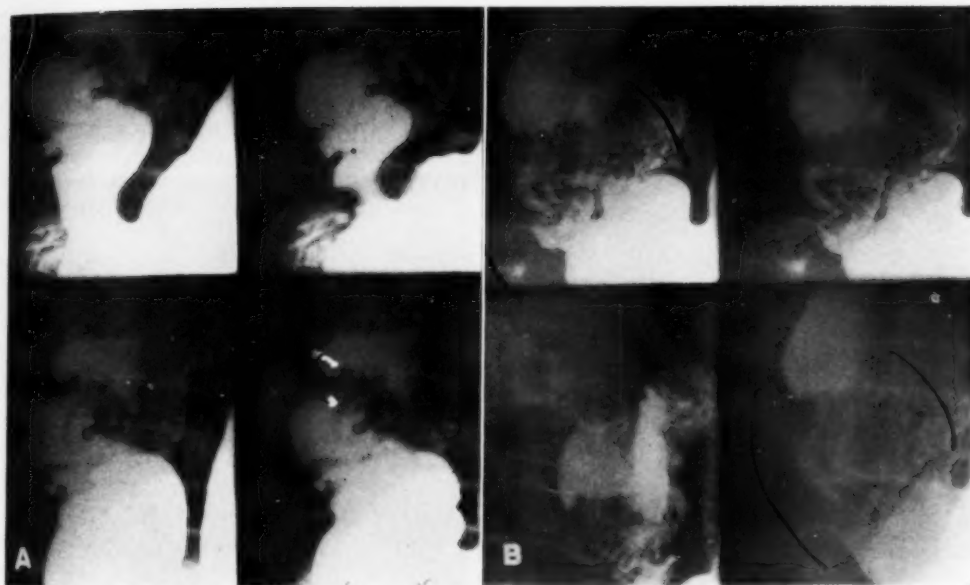


Fig. 8. Case V. Female aged 44. Representative of refusal to follow medical advice.

History: Well until severe nausea occurred after a heavy meal. Epigastric pain; vomiting of blood; tarry stools.

X-ray examination, two weeks later (A), showed prepyloric greater curvature defect suggesting ulcer. Size of lesion and age of patient pointed to a benign process.

Medical regime was suggested, but patient refused advice, changed doctors several times, and continued to have nausea, vomiting, and pain.

X-ray examination, one year later (B) showed large prepyloric defect, with palpable mass suggesting carcinoma.

Operative Findings: Freely resectable antral carcinoma, with metastasis to nodes and liver.

suspect lesion, and when the patient has been referred by a doctor who is not particularly skilled in the treatment of gastric disease, what type of x-ray report and procedural suggestions will be most helpful to the physician and most productive for the patient? It is difficult, if not impossible, to establish a set of rigid routines or policies to adhere to in handling prepyloric suspect lesions. Blood studies, fractional gastric analysis, and social and economic factors must be correlated with the history, symptoms, and age of the patient, all of which modify the problem and influence the ultimate decision. If the laboratory reports are unequivocal, and if other factors seem to point toward medical measures, the patient and family doctor must be made to understand that such treatment is associated with a risk just as is surgical intervention, because of the possibility that a carcinoma is being treated under the provisional diagnosis of benign gastric ulcer.

If, then, we have a prepyloric suspect lesion in a patient under forty who gives a history of ulcer, and gastric analysis reveals free acid in normal or high concentration, the chance of benignancy is high, particularly if the x-ray findings lean in that direction, and medical treatment may be elected.

If medical treatment is elected, under what conditions should it be given and for how long should it be continued in the presence of a suspect lesion? Gastroenterologic internists have long believed that the ideal method of treating gastric ulcer, particularly the suspect lesion, is by bed rest hospitalization under continued observation and a careful routine for a period of two weeks, to be followed by a repeat x-ray examination of the stomach. This does not imply that a satisfactory therapy procedure could not be obtained on the ambulant patient. An intelligent person whose economic and social status is such as to

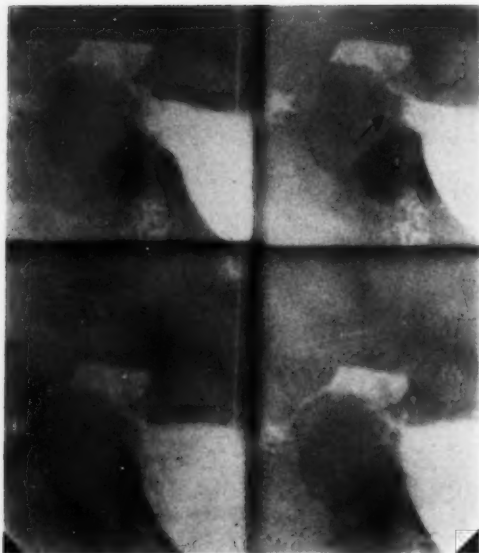


Fig. 9. Case VI. Male aged 64. Representative of error in judgment by family doctor.

History: Ulcer history past two years with gas, nausea, vomiting, and tarry stools. Family doctor treated patient for ulcer with some improvement until six months ago. More pain and nausea then developed, with no relief from medicines. Patient changed doctors.

X-ray Examination: Small prepyloric greater curvature filling defect with appearance suggesting ulcer. Cancer not excluded.

Laboratory Studies: Within limits of normal except for tarry stools.

Operative Findings: Inoperable small ulcerating cancer with metastasis to omentum, liver, and pancreas.

allow him to practice the controlled restrictions and routine of medical ulcer therapy, with the necessary repeat laboratory examinations, can be envisioned, but such a regime is not as likely to succeed, because of the usual therapeutic problems creeping into the program. When one is dealing with a problem as difficult to evaluate as a prepyloric suspect lesion, and with such serious implications, ideal conditions should be established in order to give the medical trial its optimum opportunity to succeed. This opportunity is much less likely to occur with the patient ambulatory.

If, at the end of two weeks in bed, the x-ray examination reveals a tendency towards healing, with a disappearance of symptoms and with no evidence of bleed-

ing, medical therapy may be continued in the hospital for another two weeks. If x-rays then show the lesion to be healed, the patient may be discharged, to be kept under strict medical observation for a



Fig. 10. Case VII. Male aged 52. Representative of unreliable history.

History: Well until one week earlier, when severe abdominal pain occurred, with nausea, vomiting, and abdominal distention. Vomiting of almost all food since.

X-ray Examination: Marked prepyloric greater curvature defect, with infiltration and fixation of stomach; 40 per cent four-hour residue.

Laboratory Studies: High free and combined acid with large gastric residue at one and a half hours. Other studies essentially negative.

Operative Findings: Large infiltrating carcinoma of antrum with metastases.

period of one year, with repeat x-ray studies at intervals of three months during this time.

When a regime such as the above reveals the persistence of the gastric defect at the end of one month hospitalization, the presumption of gastric cancer is high, and an exploratory laparotomy is strongly indicated.

It is obvious that any program requiring a minimum hospitalization of one month, with repeat x-ray studies, involves an economic burden of no mean proportions, and one which may be well beyond the means of

most patients. When the above routine is outlined to the patient, with due consideration of the possibility of diagnostic error or failure of medical therapy, which would then necessitate surgical intervention with its attendant risk to be added to the medical risk, the scales may well be

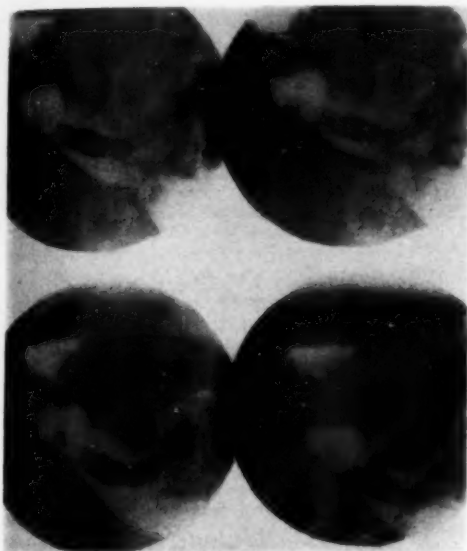


Fig. 11. Case VIII. Male aged 60. X-ray diagnostic problem.

History: Gnawing abdominal pain, nausea, vomiting; qualitative food history, duration three months. Self-treatment and family doctor treatment without relief. Weight loss of 30 pounds. No evidence of bleeding.

X-ray Examination: Large greater curvature ulcer with marked mucosal prominence; suspect carcinoma.

Laboratory Studies: Free acid 80, total 112. Other studies essentially negative.

Operative Findings: Large benign prepyloric greater curvature ulcer.

tipped in favor of surgery as the first choice.

If the patient is over forty, with a past digestive history which is equivocal and with recent indigestion associated with nausea, early satiety, and perhaps some weight loss and tarry stools, the prepyloric suspect lesion should be looked upon with utmost suspicion. If the patient's condition permits, exploratory laparotomy should be undertaken in order that an early and accurate diagnosis may be established. Surgical intervention as a diagnostic and ther-

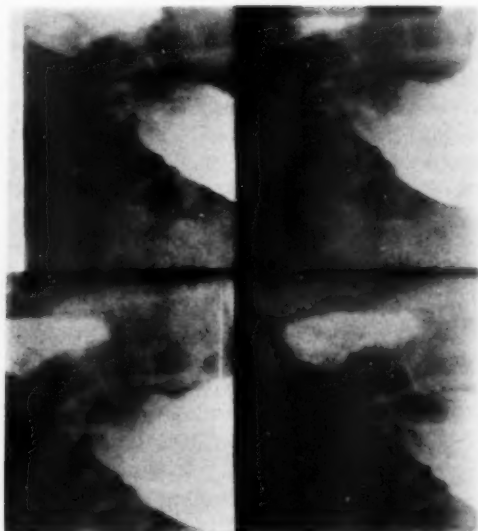


Fig. 12. Case IX. Female aged 59. X-ray diagnostic problem.

History: Epigastric fullness, nausea, quantitative and qualitative food history. Nocturnal back pain. Fifteen-pound weight loss in past six weeks, with weakness.

Laboratory Studies: Stools and chemistry negative. Free acid 15, total 32.

X-ray Examination: Prepyloric greater curvature filling defect with mucosal aberration. Tumor mass palpable. *Diagnosis:* Gastric cancer.

Operative Findings: Large mass of adhesions between gallbladder and stomach. No gastric lesion.

apeutic procedure directed toward prepyloric suspect lesions carries a morbidity of short duration and readily establishes a diagnosis.

It could be hoped that thorough and complete understanding of the significance and seriousness of the prepyloric lesion by the radiologist, and an x-ray report which would include relevant information and give as much aid as possible to the family doctor, would lead to earlier treatment of prepyloric lesions. It has been estimated that 65 per cent (1) of the failures to obtain five-year cures are due to the surgeon seeing the patient too late. *The radiologist must assume part of the responsibility for increasing the exploration and resection rate in the prepyloric lesion.*

Continued advances in gastric surgery technics, coupled with further knowledge of preoperative preparation and post-

operative care, have lowered the operative mortality for gastric resection for benign gastric ulcer in representative clinics (9) to about 2 per cent. When gastric resection can be done in the presence of gastric carcinoma, the mortality is under 6 per cent. These values must be considered and compared to the 40 per cent risk of malignancy which the patient must assume in allowing a prepyloric lesion to go undiagnosed.

In conclusion, it is suggested that a summation of the pertinent values discussed above be included with the x-ray report when the examination reveals a prepyloric suspect lesion in a patient referred by a general physician. It should be emphasized that no one finding or symptom, nor perhaps any combination of x-ray reports, laboratory studies, history, and medical therapeutic test will result in an infallible diagnosis.

The alternatives should be subject to review by the physician and patient as more information becomes available, with the final decision being made on the basis of the collected facts. It may be hoped, however, that early laboratory and clinical studies will expedite the final decision, and

that if the latter indicates surgical intervention, its prompt performance will improve the operability and curability of those prepyloric lesions which prove to be malignant.

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SUMARIO

La Lesión Prepilórica Sospechosa

Se usa el término de "lesión prepilórica sospechosa" (es decir, sospechosa de cáncer) para designar una deformidad persistente en el contorno de la zona prepilórica del estómago o una aberración del patrón de la mucosa de la misma, de tal índole que no permite hacer un diagnóstico roentgenológico absoluto. El papel del radiólogo en el plan de campaña al dar con tal hallazgo depende de la naturaleza del médico que envía al enfermo para examen. Si se trata de un médico especialmente adiestrado en los problemas gastroenterológicos, acaso baste con una descripción del tamaño y de la localización de la lesión, con sus características roentgenológicas y su relación con las funciones motoras del estómago. En cambio, si el sujeto ha sido enviado por un

médico dedicado a práctica general, el radiólogo debe facilitarle cuanta información sea posible. Hay que recalcar la gravedad de una lesión en dicha porción del estómago y que aconsejar rápidos estudios clínicos y de laboratorio, con mira a llegar al diagnóstico.

No hay ningún signo roentgenológico aislado, ni combinación de signos roentgenológicos, que indique con seguridad si una lesión prepilórica es benigna o maligna. Cuando existe una lesión prepilórica sospechosa en una persona de menos de cuarenta años con antecedentes de úlcera y un análisis gástrico que revela ácido libre a concentración alta o normal, son muchas la probabilidades de benignidad, máxime si los hallazgos radiológicos

apuntan en ese sentido, y cabe probar el tratamiento médico, de preferencia bajo vigilancia hospitalaria. Si al cabo de un mes se observa todavía la deformidad gástrica, hay muchas probabilidades de cáncer y está indicada una laparotomía exploradora.

Si el enfermo tiene más de cuarenta años, con antecedentes digestivos que son cuestionables, pero recientemente con indigestión unida a náuseas, saciedad inapetitiva, y quizás alguna pérdida de

peso y heces embreadas, hay que considerar la lesión como sumamente sospechosa y, si es posible, debe ejecutarse una exploración en el acto.

El radiólogo debe tomar sobre sí parte de la responsabilidad en lo tocante a aumentar la proporción de exploraciones y de resecciones en las lesiones prepilóricas.

Acompañanse historias clínicas y grabados para ilustrar típicos problemas planteados por esta clase de afección gastrointestinal.

DISCUSSION

Malcolm R. Hall, M.D. (Toronto, Canada): I think you will all agree that Dr. Alexander has outlined ably the radiologist's role in dealing with patients with prepyloric suspect lesions. After all, what diagnosis in medicine is infallible? Radiology is the best method of determining a correct diagnosis in prepyloric lesions short of histology.

A radiologist should be honest with himself and make a diagnosis in each given case. He should determine whether the prepyloric lesion is malignant, non-malignant, or malignant until proved

otherwise. In this last group, "malignant until proved otherwise," will be many cases of prepyloric ulcer. The patients are asked to return or are re-examined after a period of a few weeks on dietary and bed treatment. In such a patient, if the ulcer has not grossly improved, one must regard it as malignant. True, there will be patients with benign ulcers who have had inadequate medical treatment in this group. But the tendency to err will be to call benign lesions malignant rather than to call malignant lesions benign.



A Study of Gallium^{72 1}

Summary and Conclusions

MARSHALL BRUCER, M.D., GOULD A. ANDREWS, M.D., and H. D. BRUNER, M.D.²

DURING THE YEARS 1949-51, the staff of the Medical Division of ORINS spent a major portion of its effort on a study of the therapeutic use of gallium⁷². This report summarizes the problems which were encountered, the results obtained, the studies completed, and the resulting clinical judgments.

Since gallium is still a relatively unknown element and its isotopes are only rarely used in biology, the studies began with problems in physics, proceeded through chemistry, biology, and pharmacology, and ended with an assessment of clinical results.

The physical characteristics of the gallium isotopes were restudied. A method of standardization of activity was established for routine use. Methods were developed for tissue assay, and a number of new devices were set up to measure activity. Protection of personnel was a major problem. A device for remotely controlled injection of the active material was designed and built. A urine storage container was constructed, and a system of shielding certain patients was instituted. During the study, a method of preparing gross autoradiograms was developed. Microscopic autoradiograms were not satisfactory because of the short half-life of the isotope and its multiple radiations. Fifteen possibly acceptable compounds of gallium were investigated, of which the citrate proved the best.

A number of methods of preparation were used, both to purify materials for pile irradiation and for conversion to the citrate complex for animal and patient use. A method for stable gallium tissue analysis was adapted for use in long-term studies.

The toxicity of various compounds was investigated in rats, dogs, swine, and man. These studies included checking the toxicity of other dyes and reagents going into the preparation of the drug as finally used in patients.

The distribution and excretion patterns and some elements of metabolic behavior were studied in approximately 400 animals of five different species. Finally, the isotope was used in test doses in 34 patients with various types of cancer. In 21 patients full therapeutic testing was done. The main groups of patients had osteogenic sarcoma with metastases to the lung, or extensive plasmocytoma. The remainder had soft-tissue tumors, metastatic to bone.

The interpretation of the therapeutic value of gallium⁷² based upon these data is as follows:

1. *Localization of the Element:* When gallium citrate in large doses was injected into the blood stream, it rapidly accumulated in bone and viscera. About 50 per cent was excreted by the kidneys within the first twenty-four hours. Following this period, there was either a redistribution or a differential excretion of the retained material so that at five to ten days after injection there was further accentuation of the differential localization in areas of actively metabolizing bone. There were specific deposits of material in soft-tissue metastases from osteogenic sarcoma. This deposition was not uniform; instead, it was highly variable and appeared to follow not the tumor cells themselves but the sites of early calcification. Concentration of the element occurred also in areas of osteoblastic metastases in plasmocytoma.

¹ From the Medical Division, Oak Ridge Institute of Nuclear Studies, under contract with the United States Atomic Energy Commission. The summary was presented in part at the Thirty-seventh Annual Meeting of the Radiological Society of North America, Chicago, Dec. 2-7, 1951.

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and in metastases to bone from soft-tissue carcinoma. Apparently it was deposited in the immediately adjacent areas of normal bone reaction to tumor. This localization, when uniform, is theoretically excellent for therapeutic purposes, but the differential concentration in relation to visceral organs is optimal only at a time which is many days post-injection.

2. *Localization of the Radiation:* The pattern of absorption in a tissue of the radiant energy from a radioactive isotope does not necessarily follow the pattern of deposition of the chemical. About two-thirds of the total radiation from gallium⁷² is in the form of high-energy gamma emission and, no matter where the chemical is deposited within the body, there will be ionization produced in distant organs.

It takes about four half-lives for gallium⁷² to segregate significantly into localized areas of deposition within the tumor. During these first four half-lives, the chemical is distributed *via* the blood stream to nearly all tissues, but especially to the viscera. Hence, the pattern of absorption of the radiant energy in tissues will be that of total-body irradiation for an appreciable fraction of the first half-life and primarily visceral irradiation for the subsequent three half-lives.

If the assumptions and conditions of the familiar Marinelli, Quimby, and Hine formula are accepted, it is possible to calculate a first approximation to the radiation localization pattern. If the calculations are based upon uniform distribution of the isotope in 1 gram of tissue in the center of a small and a large cylinder of tissue, the proportions of energy absorbed due to the separated beta and gamma components are as follows:

	Total Radiation	Beta Energy Component	Gamma Energy Component
Human-sized cylindrical mass	100%	26%	74%
12 × 2.5-cm. cylindrical mass	100%	59%	41%

The localization in the body of that portion of the energy absorbed due to the beta component will be similar to the localization of the stable carrier chemical. No matter where the stable form is localized, however, the energy absorbed due to the gamma component is in effect a total-body irradiation. Thus, during the early hours following injection, when most of the isotope decays, the energy released favors uniform total-body irradiation. Four half-lives post-injection, when the stable form begins to show a higher differential localization in tumor than in abdominal organs, the beta component predominates in the localized area of the tumor, but there is still a considerable gamma component which gives total-body irradiation. During this period of most favorable deposition of the stable chemical, however, over 90 per cent of the radioactive atoms have decayed.

It appears from the picture of the deposition of the chemical and the pattern of ionization from the radiation that two main features must be coordinated in a radioactive chemical used for internal therapy: (a) the rate of deposition of the carrier chemical into favorable areas, and (b) the rate at which the radioisotope decays. With gallium⁷², the relative concentration of the isotope is favorable for therapy after about three to five half-lives. Iodine, for comparison, is favorably localized in less than one half-life. Since therapeutic effectiveness depends, to a large measure, upon the ratio of rate of chemical deposition to rate of decay, gallium⁷² is therapeutically ineffective.

3. *The Toxicity of the Chemical:* The toxicity of gallium citrate is relatively low in rats, but comparatively high in dogs. Man is probably somewhere in between. The knowledge gained from animal work is not transferable to man. One patient was given stable gallium in a manner which simulated the usual therapeutic trial. The dosage was continued until the toxicity picture was demonstrated but discontinued before it approached damaging levels. This patient, who received as much or more

stable gallium than most patients who were treated with gallium⁷², showed mild anorexia, malaise, and a significant lowering of the leukocyte and red cell values. From estimates of this and the clinical data, it is guessed that the LD 10 for man is about 20 mg. Ga⁺⁺⁺/kg. body weight.

4. *The Radiation Toxicity:* The clinical picture of gallium⁷² toxicity usually began with the third or fourth dose of gallium⁷² citrate at dose levels of 1.5 to 5.0 mg. Ga⁺⁺⁺/kg. given twice a week. There was first anorexia, which progressed through malaise and vomiting to weight loss greater than expected from the disease. Occasionally, especially when lower dosage was continued over longer periods, there developed a severe, dry, maculopapular, desquamating skin rash. The leukocytes began to decrease in number along with the development of malaise and progressed downward with increasing severity following each dose. Hemoglobin and hematocrit values showed a severe depression, but this developed more slowly than the leukocytopenia. After the gallium⁷² doses were discontinued, there was a continued decrease in the blood values for about one to two weeks. As the patient began to feel better, they returned to normal. With the beginning of a second course of gallium⁷² therapy, the same general picture was repeated, but at an accelerated rate and with greater severity.

It is difficult to isolate the radiation toxicity from the stable gallium toxicity, since both appear to have common features. From tissue respiration studies in a Warburg apparatus and from the clinical pictures in animals and in man, it is believed that there was a subacute total-body irradiation sickness which showed up early in the course of treatment. This was accentuated upon the later development of chemical toxicity. In cases where a major portion of the bone marrow was relatively untouched by the disease, the toxicity picture was reversible. In plasmocytoma, seriously affecting the bone marrow, tox-

icity developed more rapidly and with a greater severity and was less likely to be reversible.

Thus, it appears that there are two factors contributing to the overall toxicity of gallium⁷² used in internal radiation therapy. One is total-body irradiation; the other is metal toxicity. The two together are synergistic. Superimposed in already debilitated tissues, these two factors are sufficient to make supposed therapeutic doses lethal.

The conclusions reached on gallium⁷² do not necessarily hold true for gallium⁶⁷. Gallium⁶⁷, when given with a small non-toxic amount of carrier, may have the same favorable end distribution and has a very low energy emission. With a 3.24-day half-life, the effective radiation may be spread over a long enough period to effect a significant tumor irradiation without overwhelming total-body irradiation. There will be no chemical toxicity to augment the total-body irradiation. However, for the same reasons that gallium⁶⁷ may be more effective in tumors, it may be more lethal to bone marrow. Gallium⁶⁷ should be regarded as an entirely new problem, to which little of the knowledge gained with gallium⁷² is applicable.

CONCLUSIONS

The staff of the Medical Division of the ORINS are of the opinion that gallium⁷² is not a therapeutic agent in cancer of bone, for the following reasons:

1. Although the isotope was highly concentrated in many areas of tumor, in every case areas of low concentration occurred.
2. Because of the short half-life of the isotope, the relatively high concentration in tumors develops after most of the radiation energy has been expended.
3. Undesirable total-body irradiation effects become prominent at subtherapeutic dosage levels.
4. Development of chemical gallium toxicity was a limiting hazard in long-continued dosage.

I. Physics and Radiation Characteristics of Gallium⁷²

MARSHALL BRUCER, M.D., and H. D. BRUNER, M.D.

In 1948, Dudley and his co-workers at the Naval Medical Research Institute became interested in the toxicity of gallium and its compounds. During the course of their investigations, it was observed that this element had a predilection for bone. Gross autoradiograms, obtained following a trial use of the radioisotope gallium⁷² in rats, showed it to be localized with a high degree of specificity in areas of rapidly growing bone. The suggestion was made by Dudley that gallium might be a vehicle for carrying radiation to bone tumors.

In 1949, the staff of the Medical Division began its investigations of the pharmacological properties of gallium in animals. Much of the previous work of the Navy group was repeated, and a search was made for more suitable compounds. Methods of radioassay and standardization were restudied. By early 1950, there was sufficient evidence for beginning the therapeutic use of radiogallium in man, and in May of that year, the first patient, with terminal osteogenic sarcoma, was given gallium⁷². From May 1950 through the summer of 1951, 21 patients with metastatic tumors of a wide variety of types, mostly involving bone, were treated. An additional 34 patients were given tracer or test doses of gallium⁷².

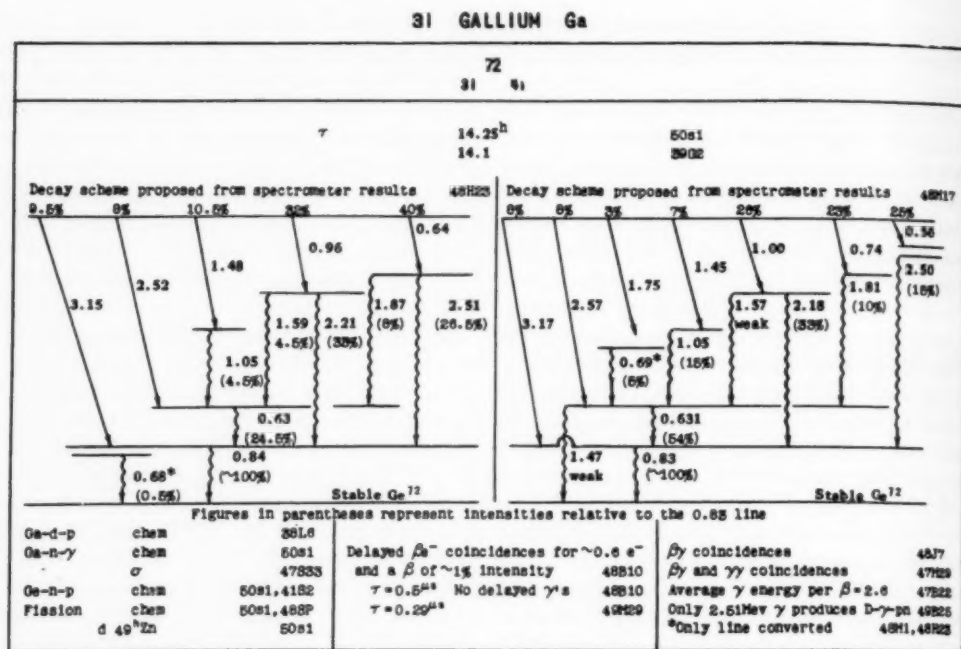
PHYSICAL NATURE OF GALLIUM

Gallium's first claim to attention was the fact that it is one of the three elements whose properties were known before the elements themselves were discovered. In 1871, it was a blank spot in the periodic table, but Mendeleef predicted its properties from its periodic relationships. It was finally discovered in 1875 by Boisbaudran in a French zinc ore. It is now known to be widely distributed in the earth's crust but always in minute quantities. There are no large deposits and present production is as a by-product of aluminum and zinc processing. Gallium

ranks fifty-seventh among the elements in abundance in the earth's crust and is present in a concentration of the order of 10^{-11} per cent. This makes it considerably less abundant than gold (10^{-9} per cent) but far more abundant than radium (10^{-13} per cent).

Gallium is a member of Group III B in the periodic table. The two higher Z members of this group have been relatively rare until recently and are not important industrially. Gallium has atomic number 31 and an average atomic weight of 69.72. In pure form it is a bluish white metal with a melting point of 29.78°C ., and a boiling point close to $2,000^{\circ}\text{C}$. Gallium differs from the usual metals in that, like water, it expands upon solidifying; the density of the liquid is 6.093 and of the solid 5.903.

There are at least ten isotopes of gallium, ranging from ^{64}Ga through ^{78}Ga . Only two of these are stable, ^{69}Ga , which is 60.2 per cent abundant and ^{71}Ga , which is 39.8 per cent abundant. The isotopes with weights 72 and 73 are found in minute amounts in uranium fission products. Of the eight artificially produced radioactive isotopes, four have half-lives measured in terms of minutes, one five hours, and one nine hours; all of these are useless therapeutically. The experience gained from working with 14-hour Ga^{72} indicates that a 14-hour half-life is at the lower limit of practicability for isotopes to be used in patients. Thus, of all the gallium isotopes, only the 14.30-hour Ga^{72} and the 78-hour Ga^{67} are useful. The preferable Ga^{67} isotope can be made with a ($p, 2n$) reaction that is efficient only with high-energy protons, but when this project began no cyclotron was available to us for the production of protons of this high energy. The Ga^{72} isotope can be made either with fast or thermal neutrons. The fast neutron reaction has an unknown, but probably low, cross section and would demand the use of separated Ga^{73} . Therefore a thermal neutron

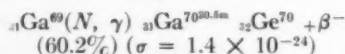
Fig. 1. Two alternative partial decay schemes for Ga⁷².

reaction was the only feasible method of production at the beginning of this project.

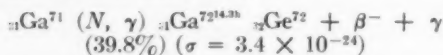
The activation equations for the thermal reaction are as follows, where A equals specific activation, N the number of target atoms, σ the cross section (Th-n), f the neutron flux, t the irradiation time, and T the half life.

$$A = N\sigma f \left(1 - e^{-\frac{0.693t}{T}} \right)$$

For ³¹Ga⁶⁹ as the target,



For ³¹Ga⁷¹ as the target,



Thus, there will be roughly 1.7 times more Ga⁷² formed than Ga⁷⁰, and within three hours after removal from the neutron flux, the twenty-minute Ga⁷⁰ activity will be less than 1 per cent of the total.

Of the seventy thermal neutron-produced isotopes with half-lives falling be-

tween twelve hours and sixty days, Ga⁷² is twenty-first in rank of efficiency of production. Its low cross section predicts that the specific activity will be low, and under the best present conditions there is obtained 1 mc. of Ga⁷² per 4.7 to 5.2 mg. of stable gallium. Separated Ga⁷¹ is available, and with its use the specific activity can be increased fourfold, but this is still insufficient for practical purposes. A higher neutron flux would greatly improve the specific activity problem, but such reactors are not generally available, and the low-specific-activity material (1 mc./5 mg. Ga^{69,71}) had to be used in this project.

Two alternative partial decay schemes for Ga⁷² are shown in Figure 1. The predominant elements of decay as stated by Haynes *et al.* (1) are shown in Table I. The probable dosage rate in terms of gamma intensity has been calculated for the major components of the decay scheme as shown in Table II.

Obviously a considerable portion of the

energy is discharged as high-energy gamma emission. Such an isotope, no matter where located in the body, must yield considerable total-body irradiation. It can be calculated that in terms of the radiation energy absorbed from a uniform dosage throughout the tissues of man, the ratio of beta to gamma components would be about 20 β to 58 γ . This relationship will be reversed in a small animal such as the rat. Therefore, there can be no direct transference of radiation dosimetry from smaller animals to man.

TABLE I: PREDOMINANT ELEMENTS IN DECAY OF Ga⁷²

Predominant Beta Rays		Predominant Gamma Rays	
Energy (mev)	Frequency (%)	Energy (mev)	Frequency (%)
3.15	9.5-20	2.51	26
2.52	8.0-18.5	2.21	31.5
0.95	32	1.87	7.5
0.64	40	1.59	4.5
		1.25	2
		1.05	4.5
		0.84	100
		0.68	2
		0.63	18.5

The beta-ray dosage was calculated from the formula of Marinelli, Quimby, and Hine: $D\beta = 88 E\beta TC$ where E equals the mean energy of the beta rays weighted by their frequency, T the half-life in days, and C the microcuries disintegrating in 1 gram of tissue. By this formula, the beta dosage was calculated at 20.62 rep/mc. of Ga⁷² completely decaying in 1 gram of tissue. Similarly, we used the formula $D\gamma = K\gamma Cg$, where $K\gamma = 1.44 t \times 10^{-3}$, t is the half-life in hours and g is a calculated geometric factor. Using weighted frequencies and mean energies, the gamma-ray dosage for a standard size man equals 58.41 r/mc. of Ga⁷² (complete disintegration) in 1 gram of tissue in the center of the body. This roentgen dosage is based upon uniform distribution of gallium throughout the body so that the radiation cross-fires the given gram of tissue in the center of the body. The same dosages calculated for the rat are 14.45 r for the gamma component, while the beta dosage remains the same as that for man.

TABLE II: RADIATION INTENSITY OF COMPONENTS OF THE DECAY OF Ga⁷²

Gamma (mev)	I γ r/mc.-hr. at 1 cm.	Per Cent Frequency	I γ Contribution to Total γ -Radiation I $\gamma \times \% / 100$
2.51	11.25	26.0	2.925
2.21	10.25	31.5	3.229
1.87	9.3	7.5	0.697
1.59	8.3	4.5	0.373
1.25	6.9	2.0	0.138
1.05	6.0	4.5	0.270
0.84	4.9	100.0	4.900
0.68	4.1	2.0	0.082
0.63	3.8	18.5	0.703
TOTAL			13.317 r/mc.-hr. at 1 cm.

Since autoradiographic studies have shown that gallium is not uniformly distributed even in small volumes of tissue, and since the metabolic pattern continuously undergoes rapid change during disintegration of gallium, these calculations are of limited usefulness and are to be interpreted as order-of-magnitude values in assessing the radiation dosage to tissues. Three other methods of estimating radiation dosage which were based on measurements external to the body were investigated, but all were inadequate for the same reasons that calculated dosages were inadequate. By default, therefore, the hematological picture appeared to be the most practical method of assessing the radio-toxic effects of therapeutic amounts of Ga⁷².

STANDARDIZATION OF GALLIUM

A detailed statement of standardization methods for Ga⁷² has been published as ORO-44 by the Technical Information Service, USAEC (2). Briefly, two methods were described, an electroscopical calibration using gamma radiation and a comparison of the beta rays against an Ra DEF standard.

A Lauritsen electroscopical was calibrated against a known source of radium and converted to millicurieage by use of specific gamma roentgen intensities by methods described by Marinelli, Quimby, and Hine

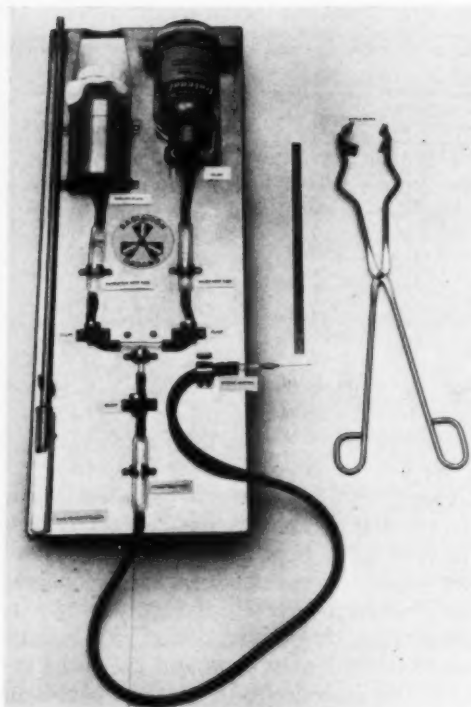


Fig. 2. Special intravenous injection system. For detailed description, see text.

(3). Similar measurements were made on a source of Ga^{72} and the calculation based upon the $I\gamma$ value computed above from the incomplete but best available decay scheme described by Haynes.

A beta calibration against a U. S. Bureau of Standards Ra DEF standard was run a number of times as a check on the electroscope standardization. Beta absorption curves were run on samples with constant geometry and all sources of variations kept to a minimum.

HEALTH PHYSICS

The dosages employed in patients were at first 10 to 20 mc. repeated weekly. After a time they were increased to 50 to 100 mc. repeated twice weekly. With the development of severe toxic reactions, the dosages were reduced to the 40- to 50-mc. range repeated twice weekly. During the entire period of this study 12 curies of Ga^{72} were used.

There were four main sources of radiation hazard which demanded special attention. The first was the area surrounding the chemical preparation of the gallium nitrate as it arrived from the reactor. The second was during the injection of the material into the patient. The third was around the patient for the subsequent twenty-four hours, and the fourth was the collection of excreta saved for analysis.

To reduce radiation dose during chemical preparation of gallium for patient use, special 6-inch lead shields were constructed inside each of two fume hoods which were used alternately. The highest total body dosages received by the chemists averaged about 55 mr/day, but this low level was achieved only after considerable redesign of the handling procedures.

Since it was necessary to inject gallium by the intravenous route, supratolerance dosages were received by personnel until a special intravenous injection system was devised, as shown in Figure 2. This device has since been found practical for use with almost all intracavitary or intravenous injections.

The infusion apparatus was designed to be autoclaved as a unit, set up at the bedside, and operated from a distance. A standard parenteral fluid bottle was fastened to the board at a slightly higher level than the shielded wide-mouth flasks. The two flasks drained by gravity into parallel visual drop tubes; these in turn drained through a T-tube into the common drop tube, which was connected by rubber tubing to an intravenous needle. Tubing clamps were placed so as to control the drainage of either flask into the intravenous needle or to allow the saline to back-up into the shielded flask for rinsing. On each tubing clamp there was fitted a 1/4-inch hexagonal nut which fitted a hex spintight wrench fixed on the end of a 3-foot wand.

In operation, the radioactive solution was kept behind shielding while the saline infusion was started. When the infusion was flowing at a slow steady drip, the radioactive solution was poured into the open-

mouth flask. The usual safe distance from this time on was 3 to 4 meters from the apparatus. By means of the wand, the rate of mixture of radioactive solution and saline was controlled from 3 feet, and the body was about 5 feet away. Since the radioactive fluid was tinted by a pH indicator, the rate of flow through each drop tube and the color intensity of mixture in the common drop tube could be observed from across the room. The usual infusion took ten to thirty minutes. When all of the radioactive solution had drained from the shielded flask, the common clamp was closed and the saline was washed back into the flask. This rinse and two subsequent rinses were allowed to run into the vein without further dilution by saline. With three rinses, the residual activity in the shielded flask and tubing was negligible and the apparatus could be safely removed from the room. The entire assembly was washed, reassembled, and sterilized in an autoclave as a complete unit ready for the next use.

With all other methods of injecting radioactive materials, the period of injection was found to be the time of maximum exposure of nurses and staff. By use of this apparatus, the injection exposure became a relatively innocuous procedure.

The third area of radiation hazard was around the patient. Measurements of the 6.25 mr/hr. isodose lines around the patient at various times after injection gave patterns of which an example is shown in Figure 3. Immediately after injection of 20 mc. of Ga⁷² citrate, this isodose line is approximately a circle 4 meters from the center of the patient. Because Ga⁷² has a short half-life and is excreted rapidly via the urine, the isodose line rapidly regresses toward the patient. By two hours the maximum permissible isodose line is 3 meters from the patient, and by sixteen hours 1 meter. After two days it is close to the surface of the body so that there is little hazard to the nursing personnel carrying on ordinary hospital routines.

Since ordinary plaster walls provide almost no shielding, all personnel were kept

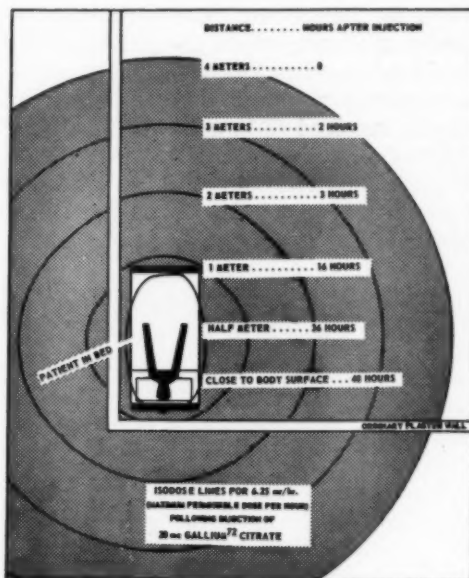


Fig. 3. Isodose lines for 6.25 mr/hr. following injection of 20 mc. gallium⁷² citrate.

away from adjacent hallways and ward rooms during the initial period after injection. Other patients having radioactive therapy probably received a negligible fraction of their own dosage from exposure to a gallium patient, but patients not under radioactive therapy and staff members were shielded from active patients. A detailed statement of the health physics precautions taken for gallium and other isotopes in the Medical Division Hospital has been published (4).

During surgical operations, a radioactive patient may provide a considerable spot dose to personnel who acquire doses approaching tolerable limits during their routine work. For example, during a two-and-one-half-hour operation to remove the left lung of a patient who had been given a 20-mc. test dose of Ga⁷², the surgeon and his first assistant each received a total of 400 mr to their hands as measured on film badges placed within the palms of their rubber gloves. Badges under their collars registered 30 mr. The anesthetist for this operation received a total-body exposure of 40 mr.

During the chemical preparation of Ga^{72} citrate, the exposure to the hands can be considerable. During the hour required to prepare 4 ampules of Ga^{72} citrate, the chemist received 530 mr to his right hand and 355 mr to his left. During autopsies on patients who had been given radioactive gallium just prior to death, total-body exposure to the pathologist was as high as

two or three patients gave a continuously supratolerable level within a radius of 4 meters. In order to contain this radiation, a urine storage vault (Fig. 4) was built.

ASSAY AND SAMPLE COUNTING PROCEDURES

A standard pseudo-wet-ashing procedure was used to estimate the amount of radiogallium in tissue samples. A weighed



Fig. 4. Urine storage vault.

628 mr over the two- or three-hour procedure.

One of the major sources of radiation hazard was from the area set aside for storage of urine collected from active gallium patients. During the first twenty-four hours after injection, up to 50 per cent of the injected dose of Ga^{72} was excreted, so that twice-weekly collections on as few as

amount of tissue was placed in a 10-ml. volumetric flask. Concentrated HNO_3 was added and heated gently until the tissue was completely dissolved. Water was added to volume and the contents were then poured directly into the top half of a 50-mm. standard Petri dish. Previous studies had indicated that there was no preferential distribution of Ga^{72} into fat

globules. A standard survey meter can be used to estimate the amount of activity in the 10-ml. volumetric flask in the event that dilution is necessary in order to obtain counting rates between 300 and 3,000 per minute.

The sample was placed in a carriage which slid with reproducible geometry beneath a Geiger-Müller tube mounted in a horizontal lead shield. The tube was a 30 mg./sq. cm. glass envelope carbon cathode tube sold by Herbach and Rademann, Philadelphia.

The usual standardization procedures were used to equate counts per minute to millicuries. The efficiency of counting was routinely between 1.55 and 1.80 per cent. Efficiency of counting was sacrificed for precision of counting plus speed and ease of preparation of large numbers of samples. Only one transfer of a sample was necessary in this procedure, and only two pieces of glassware were exposed to contamination. The apparatus was easily cleaned with Dreft or Tide, but not with ordinary soap powders.

Certain special instruments were devised for routine counting procedures. The urine of patients contained large quantities of Ga^{72} during the first twenty-four hours,

so that extreme degrees of dilution were required for conventional counting methods, and in the process there was appreciable personnel exposure. For this reason the following system was devised:

A d.c. electrometer for amplification of ion chamber currents was connected to an ion chamber especially built for urine measurements by Mr. Floyd M. Glass of the Instruments Division, ORNL, Oak Ridge. The urine was collected in 2-liter machine-made Pyrex bottles; at the end of the collection period, water was added and mixed to the 2,000 c.c.-mark. The bottle was placed in a lucite rack in constant geometrical relationship to the ion chamber. The readings of the electrometer at different range scales were made directly as millicuries of gallium according to direct calibration from samples of known millicuriage. The range of accurate readings was from 10 microcuries to 35 millicuries total in 2,000 c.c. The precision was of the order ± 2 per cent.

The method involved no transfer, no dilution, and a minimum contamination of glassware. The daily samples could be measured in a tenth the time necessary with conventional methods, and with negligible exposure of personnel.

II. Gallium Chemistry of Biological Interest

JESSE D. PERKINSON, JR., PH.D.,¹ JAMES S. ELDRIDGE, B.S., and BETTY M. COOPER, M.D.

The primary problem in the chemistry of gallium was related to finding a compound both biologically acceptable and easily synthesized at high levels of radioactivity.

BASIC CHEMISTRY

Because gallium has only recently become available in a pure state, relatively little is known of the chemistry of this element. Its chemical properties are quite similar to those of the more widely known aluminum. Its usual valence is +3, but

stable +2 salts and a +1 oxide are known. The metal is stable in air but an oxide film forms in moist air or oxygen. Gallium is relatively resistant to both alkali and acid but, when heated with a mixture of HCl and HNO₃, it will slowly react to form the chloride. Several salts can be made by the direct action of halides in the presence of heat. The sulfides, sulfates, nitrate, and phosphate have been formed, as well as a few organic salts. A sesquioxide is produced by heating a gelatinous hydroxide of uncertain structure between 900 and 1200°.

Most gallium salts are hydrolyzed in aqueous solution and can be kept in solu-

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tion only when strongly acidic or basic. This is particularly true of the inorganic salts (5).

In choosing a compound suitable for toxicity and distribution studies and for patient use, the work of Dudley and Levine (6) was most helpful, although several compounds were studied in addition to those prepared by these investigators. The criteria used for acceptability of possible compounds were:

- (a) Complete solubility in water and 0.9 per cent NaCl solution at 20 to 42° C.
- (b) Stability of the solution.
- (c) Low rate of release of gallium ions after injection of the compound into animals.
- (d) Ability of experimental animals and man to metabolize safely the non-gallium moiety.
- (e) Production of a sterile compound.
- (f) Speed of synthesis from gallium nitrate.

With these criteria, the complexing abilities of several acids and bases were studied. Hydrochloric, carbonic, phosphoric, ascorbic, maleic, tartaric, acetic, salicylic, oxalic, benzoic, and succinic acids and ethanolamine and diethanolamine were unsatisfactory. The complexes formed with gluconic, mandelic, and lactic acids were suitable in that they remained in solution at a pH range of 7.2 to 7.6 but were undesirable otherwise (7).

The compound that was decided upon for animal and human studies was gallium citrate. One of the chief reasons for choosing this compound was the fact that it could be prepared quickly and easily in sterile solution. The final solution could be administered within two to three hours after the bombarded gallium nitrate was removed from the nuclear reactor.

STABLE GALLIUM CITRATE

All of the stable gallium citrate used in the accompanying studies was prepared according to the method of Dudley (8), with a few unimportant modifications. Analyses of several batches of this compound gave a gallium content of 23 to 24

per cent as contrasted with the 25 to 26 per cent value reported by Dudley.

RADIOGALLIUM CITRATE

Purified gallium nitrate was prepared according to Dudley (8) and sealed in quartz ampules, which were scored around a slightly indented neck. When the bombarded material was received, the ampule was placed in a plastic holder and the top was removed by hitting the scored neck a sharp blow. For each 300 mg. of gallium as the nitrate, 4 ml. of 6 *N* HCl was pipetted into the ampule. A heat lamp was placed over the ampule and the solution was stirred by drawing the material into a pipette and allowing it to flow back. When the solution appeared complete, the material was filtered. Filtration was necessary because quite often one or two small particles would not dissolve under these conditions. While the nature of these particles was not determined, it was thought that they were small amounts of the relatively insoluble oxide. The ampule was rinsed once with 1 ml. of 6 *N* HCl and twice with 2 ml. of water. The washings were also filtered. The total filtrate was added to a mixture of 8 ml. of 20 per cent citric acid solution, 3 ml. of a saturated water solution of bromocresol purple and 15 ml. of chloretone solution (5 mg. per ml.). This mixture was agitated by an air stirrer. A solution of 15 *M* NaOH was added dropwise until a definite purple color was produced. A final pH of approximately 7 was determined by means of pH paper. The average gallium concentration in the final preparation was 9.6 mg. per ml. The solutions and glassware used were carefully cleaned and sterilized by autoclaving, so that the final product was aseptic.

When the solutions of this radiogallium citrate stood for a few days, a definite Tyndall effect was seen, and it became more pronounced with prolonged standing. Several weeks after preparation, there was a definite precipitate. Because of these facts and the nature of the animal distribution of the gallium, the possibility that at least

part of the gallium citrate was in a colloidal form continued to be a problem throughout all of the animal and human studies. No attempts were made to determine whether any of these small colloidal particles were present in the freshly prepared solutions, but all indications were that they did exist.

ION-EXCHANGE GALLIUM CITRATE

The possibility of the formation of colloidal particles and the knowledge of the ease with which gallium is hydrolyzed led to a study of another method of synthesis of radiogallium citrate (9). As has been pointed out, the ion-exchange method of preparation was desirable in all respects except that the mol ratio of citric acid to gallium was 5 to 1 as contrasted with a ratio of 1.2 to 1 for the simple radiogallium citrate preparation. While the distribution and excretion of the ion-exchange complex was somewhat different from that of the

simple prepared complex, this difference might have been due to the greater amount of citric acid rather than to a difference in the degree of hydrolysis. Whatever the reason, the complex formed by ion-exchange was impracticable because of the high citric acid concentration of the solution.

CHEMICAL GALLIUM DETERMINATION

The method used for the analysis of gallium in tissues was based on that of Dudley (10). The original method was for 5- to 10-gm. samples of tissue, while the sample size used in obtaining the results in the accompanying reports was 0.5 to 1.5 gm. The reagents were reduced in the same proportion. It should be added that reliable results were obtained only when the chloroform extractions of gallium were made by ten minutes of mechanical shaking.

III. Effect of Internal Irradiation on Respiration of Rat Liver Slices⁴

JESSE D. PERKINSON, JR., PH.D., and ROBERT S. INGOLS, PH.D.

Since there exists no means of determining the radiation dosage derived from an internally administered radioisotope except by use of calculations such as those of Marinelli, Quimby, and Hine (3), it seemed desirable to find some measurable biological effect of radiation which could serve as a basis for comparison of the effectiveness of different isotopes and perhaps of external roentgen irradiation. The results reported here are from a preliminary attempt made to determine whether the inhibition of total tissue respiration, or oxygen consumption, was proportional to the amount of internal irradiation that the tissue received.

Gallium⁷² was used as the source of internal radiation because of the interest in this isotope as an irradiator of bone tumor.

Since it had been shown that gallium concentrates significantly in the liver (11), knowledge concerning the effect of the metal and of radiation from the isotope was desired. The decay scheme for Ga⁷² is incomplete, so that a true roentgen equivalent physical (rep) value for radiation dose was impossible (12). The liver of the rat was used because of the relatively extensive data available concerning the effect of physiological variables such as age, weight, and sex on the metabolism of that tissue. A large accumulation of data exists concerning distribution of gallium in the liver (13).

Barron (14), in 1946, was apparently the first to show conclusively that whole-body roentgen-irradiation of rats inhibited the oxygen consumption of liver slices and that some enzymatic systems were more sensitive than others. Until that time the literature was quite confused.

There is a paucity of reports concerning

⁴ From the Department of Public Health and Biology, Georgia Institute of Technology, Atlanta, Ga. This work was done at the ORINS, Oak Ridge, Tenn., Research Participation Program.

the metabolic effect of internally administered isotopes. Barron *et al.* (15) studied the effect of intravenously injected plutonium on the metabolism of several tissues. They found that some phases of liver metabolism were inhibited in two series of rats that had received either 1 or 2 mg. of $\text{PuO}_2(\text{NO}_3)_2$ per kilogram and were killed two to ten days later. In other series, however, the same inhibitions were not observed. Barron suggested that the apparent lack of relationship between radiation dose and degree of metabolic inhibition might be attributable to an unequal distribution of plutonium and to the relatively shallow penetration of alpha rays.

ACUTE EXPERIMENTS

Experimental: Male Wistar-Carworth strain rats weighing between 200 and 250 gm. received by tail vein either a mixture of stable gallium and gallium⁷² citrate or stable gallium citrate alone, so that all animals received equal amounts of metal. Amounts of Ga^{72} equivalent to 1.7 mc. per kilogram were injected as accurately as the solution volumes could be measured with a tuberculin syringe. The injections were made with the rats under light ether anesthesia and just after 0.2 ml. of 10 per cent calcium gluconate solution was given, as described in Section IV of this series.⁶ At two, six, twelve, eighteen, twenty-four, forty-eight, seventy-two, and ninety-six hours after injection, one animal which had received Ga^{72} and its stable gallium control were sacrificed and the livers removed. Portions of the same lobe of each liver were used for QO_2 , glycogen and water content determinations and for histologic studies and activity measurements. It was determined that the anesthesia and injection technic did not affect the QO_2 . Twelve rats were anesthetized with ether and injected by tail vein with calcium gluconate and saline equal in volume to that administered to the rats that received gallium citrate solutions. At six hours after

TABLE III: LIVER QO_2 VALUES FOR UNTREATED RATS AND THOSE THAT RECEIVED EITHER STABLE GALLIUM PLUS Ga^{72} OR ONLY STABLE GALLIUM.*

(Number of animals used to obtain the average values are in parentheses)

Time (hr.)	P	Stable QO_2	P	Radio-active QO_2	P
2	<0.01	4.9 (4)	<0.20	5.3 (4)	<0.01
6	<0.01	5.6 (7)	<0.02	4.2 (7)	<0.01
12	<0.02	6.8 (4)	<0.04	5.1 (4)	<0.01
18	<0.01	7.6 (4)	<0.01	5.0 (4)	<0.01
24		6.1 (12)		5.8 (12)	
48		6.3 (4)		6.5 (4)	
72		6.7 (4)		5.7 (4)	
96		5.9 (4)		6.2 (4)	

* Normal QO_2 = 6.2 av. (22)

injection the liver slice oxygen consumption was not different from that of the untreated normal animals.

All rats used in these studies received a stock diet of Rockland Checkers *ad libitum*.

One interest in these studies was the possible application of the results to the use of Ga^{72} in human beings, so that the rats were not fasted, as they usually are before QO_2 determinations, since the patients would not be in a fasting state. It has been shown that glycogen acts as a metabolically inert substance in liver QO_2 determinations (16). In measuring liver QO_2 and glycogen content of 22 untreated rats, it was found that consistent QO_2 values could be obtained by making an empirical correction for the glycogen content, so that all values are reported with this correction.

The QO_2 determinations were made with standard Warburg technics, using Krebs-Ringer phosphate buffer solution in a saturated O_2 atmosphere. No substrate was added. The data from four or five flasks with slices from the same liver were averaged for each QO_2 value.

Results: 1. QO_2 Determinations: The average QO_2 for untreated normal rats of the same age, weight, and sex as the control and experimental animals was found to be 6.2 $\mu\text{l. of O}_2$ per milligram of dry weight tissue per hour. In Table III, the number of animals killed at each period after injection is given in parentheses together with the probability values for the statistical

⁶ Page 551.

TABLE IV: QO_2 VALUES FOR RATS RECEIVING STABLE AND RADIOACTIVE GALLIUM

("Mg./kg." refers to the average amount of gallium that was injected)

Hours	Stable		Radioactive	
	QO_2 (gly)	mg. Ga/kg.	QO_2 (gly)	mg. Ga/kg.
2	4.9	8	5.3	8
6	5.6	9	4.2	9
12	6.8	9	5.1	9
18	7.6	9	5.0	8
24	6.1	10	5.8	10
48	6.3	12	6.5	10
72	6.7	9	5.7	9
96	5.9	8	6.2	9

animals. It can be seen that the differences between the values for the untreated animals and those receiving either the stable gallium or Ga^{72} plus stable gallium are highly significant through the eighteen-hour period. The differences between the stable gallium and the Ga^{72} plus stable gallium values are significant at six, twelve, and eighteen hours after injection.

The QO_2 and radioactivity data summarized in Figure 5 show that the stable gallium alone had an inhibitory effect on the oxygen consumption for six to twelve hours

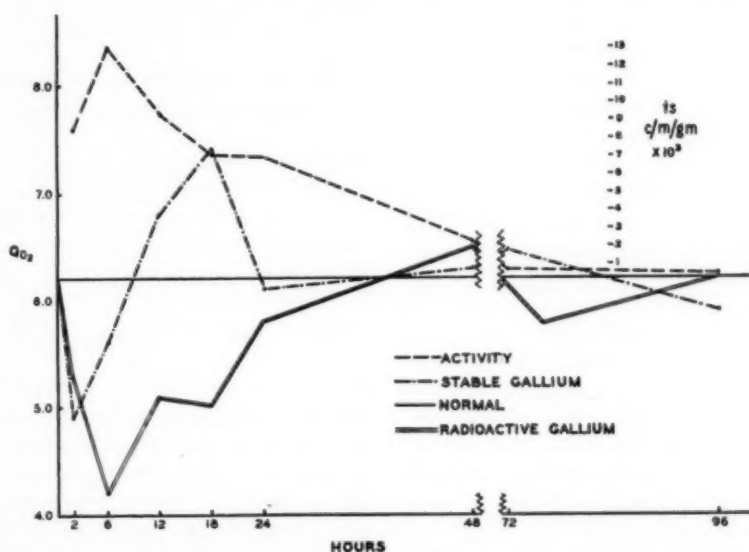


Fig. 5. Change in QO_2 following administration of stable and radioactive gallium. "ts" refers to the fact that the activities are those that existed in the liver at the time of sacrifice.

validity of the differences found. These probabilities were calculated according to "Student's" formula. The left-hand "P" column refers to the differences between the QO_2 's for the animals that received only stable gallium and the value for the untreated normal animals. The center column refers to the differences between the stable gallium control animals and those receiving radioactive plus stable gallium. The right-hand column refers to the differences between the rats that received radioactive gallium plus stable gallium and those for the untreated normal

after injection but that the Ga^{72} plus stable gallium produced a still greater decrease in the QO_2 and that the inhibition persisted for eighteen to twenty-four hours. The radioactivity of the liver samples is expressed as counts per minute per gram of tissue at the time the animals were sacrificed. The obvious proportionality between the QO_2 and the activity present at the time of sacrifice is seen better in Figure 6, where QO_2 is expressed as a function of activities. That the QO_2 differences were not due to different doses of gallium can be seen in Table IV, where it is shown that the amounts of gal-

TABLE V: GLYCOGEN CONCENTRATIONS IN LIVER FOLLOWING GALLIUM INJECTION

Hours after Injection	Per Cent Glycogen in Liver	
	Stable Gallium	Radioactive plus Stable Gallium
2	1.7	2.0
6	0.8	0.7
12	1.6	1.9
18	4.1	2.1
24	3.9	2.0
48	2.7	3.1
72	4.8	3.1
96	4.8	4.2

liver were essentially the same for the experimental and control animals.

2. *Histology:* There was no evidence of histologic abnormality in any of the liver sections.

3. *Glycogen and Water Content:* In Table V are shown the average glycogen concentrations in livers from animals sacrificed at the different time intervals. It can be seen that the glycogen content was lower in both the irradiated and non-irradiated livers for the first twelve hours after injection, but that this lower level persisted longer in the rats that received the radiation. While the trauma due to the injection procedure and the gallium itself may have affected the liver glycogen store, the radiation had an additional effect.

There was no measurable effect of either the gallium or the radiation on the water content of the liver.

CHRONIC EXPERIMENTS

Experimental: Since the radiation derived from Ga^{72} inhibited the liver oxygen consumption up to twenty-four hours after injection, it was important to learn whether repeated injections of stable and radioactive gallium would have a more permanent effect. Since such an experiment would give information as to whether untoward reactions in patients who received Ga^{72} were due to the chemical toxicity of gallium or to radiation combined with chemical toxicity, 8 male Wistar-Carworth rats weighing between 200 and 250 gm. were injected by tail vein twice a week for four weeks with an average single radiation dose of 1.7 mc./kg. so that they received an av-

erage total of 14.5 mc./kg. The average single gallium dose was 9 mg./kg. or an average total of 75 mg./kg. Eight other rats were injected according to the same schedule with equal amounts of stable gallium. All rats had free access to food and water. In order to obviate the already demonstrated twenty-four-hour period of inhibition of liver oxygen consumption that resulted from Ga^{72} radiation, these rats were sacrificed ninety-six hours after the last injection and the QO_2 of sliced liver sections determined as in the preceding experiments. Stable gallium content of the same liver lobe was determined for all animals.

Results: The average results of these repeated doses are presented in Table VI,

TABLE VI: AVERAGE FINDINGS AFTER REPEATED GALLIUM INJECTIONS

	Stable Gallium	Radioactive plus Stable Gallium
QO_2	5.1 (4.3-5.8)	5.1 (4.6-6.0)
W.B.C.	15,000 (10,000-18,000)	9,800 (7,000-13,000)
Hb.	13(12-14)	13(11-17)

with the ranges in parentheses. The QO_2 was inhibited to the same significant degree in the animals that received the stable gallium as in those receiving Ga^{72} plus stable gallium. The radiation produced no effect that lasted as long as ninety-six hours after the last injection, while the accumulated gallium did inhibit respiration at that time.

As shown in Table VI, the radiation from Ga^{72} produced a mild leukopenia, while the stable gallium was without effect. The hemoglobin was reduced to the same degree in both groups of rats, so that this amount of radiation did not affect hemoglobin production, while gallium inhibited it.

Liver damage could not be seen histologically.

The irradiated rats lost weight during the four-week experimental period with the exception of one animal that gained a total of only 8 gm. The average weight loss was 26 gm. Five of the stable gallium

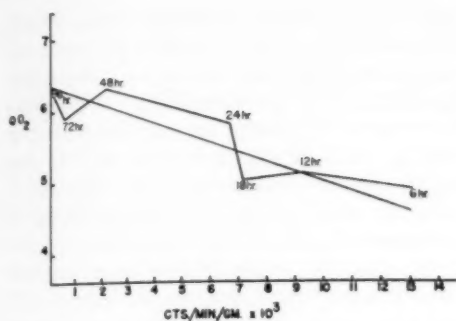


Fig. 6. Relationship between Q_{O_2} and gallium activity. The activities in counts/min./gm. $\times 10^3$ are those that existed in the livers at the time of sacrifice.

rats lost weight but the average weight loss was only 2 gm. In the irradiated rats diarrhea occurred an average of sixteen days after the first injection, while in the stable gallium rats this symptom did not develop until the twenty-fourth day.

The average gallium content of the stable gallium rat livers was 2 μ gm. per gram (range, 2-3) and that of the irradiated rat livers was 4 μ gm. per gram (range 1-7).

DISCUSSION

These experiments were made in an attempt to learn whether a biological effect of radiation might be used as a basis for comparing one internally administered radioisotope with another. No attempt has been made to arrive at any physical expression of radiation dose.

Figure 6 is presented as a general statement of the relation that was found to exist between the relative amount of radiation present at the time the rats were sacrificed and the effect of the radiation on total oxygen consumption by the liver. Several factors enter into this statement. It is obvious from Figure 5 that the liver tissue recovers quickly from the effect of this amount of radiation, so at all times there is a recovery process which influences the overall measurement. Since the peak of gallium concentration is reached sometime between two and twelve hours (Fig. 5), the decrease of gallium content, and therefore of radiation dose, after that time will pro-

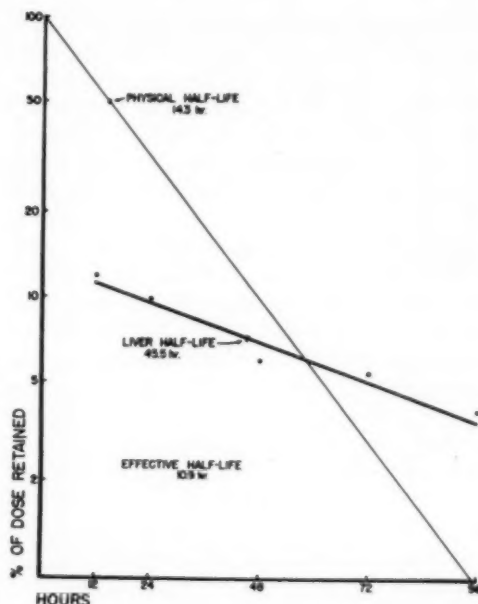


Fig. 7. Biological half-life of gallium⁷³ in liver. The effective half-life was calculated according to Marinelli *et al.* (3).

duce less inhibition of the oxygen consumption.

In Figure 7 is shown the physical decay of the Ga^{73} . Not only is the gallium concentration in the liver beginning to decrease sometime during the six- to twelve-hour period, but what gallium is there is contributing less radiation per unit weight from the moment it is injected.

An examination of Figure 8 shows that sometime during the eighteen- to twenty-four-hour interval the decrease in liver activity becomes chiefly a function of the physical decay of Ga^{73} . It is interesting to note that the Q_{O_2} inhibition is evident until this same time.

Considering the fact that the total oxygen consumption is the sum of many different metabolic reactions, it is understandable that a correlation between amount of internal radiation and the Q_{O_2} would not be completely consistent from measurement to measurement. As Barron has shown, some enzymatically controlled reactions are more sensitive than others (14), so

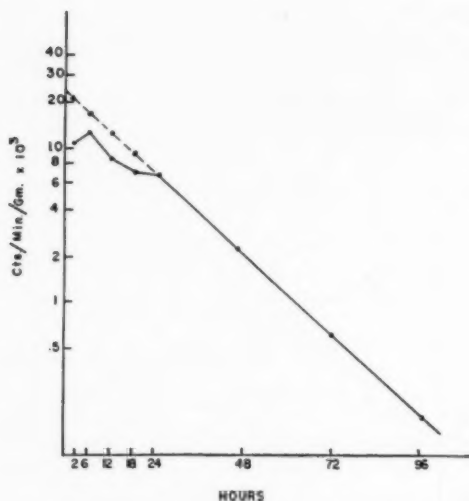


Fig. 8. The stability of gallium concentration in the liver. The solid line is an expression of the determined activity in liver at the indicated times after injection. The broken line was obtained by extrapolating the constant part of the activity curve. Activities calculated by means of the decay constant for Ga^{72} are shown to be in agreement with the extrapolation.

that it is possible that a single enzyme system could be more strictly correlated with the amount of radiation. With this idea in mind, experiments are being conducted to learn at what level of internal P^{32} irradiation liver QO_2 's are minimally and maximally affected. With this background, it is planned to study the effect of the minimal amount of P^{32} radiation which will affect different enzyme systems and to compare these results with the effects of other internally administered isotopes.

It was possible that the radiation from

Ga^{72} might not have produced an inhibition of oxygen consumption without the presence of gallium. In order to test this possibility, Ga^{67} , with a specific activity of essentially 100 per cent, is being used in similar studies. The results so far obtained show that the internal radiation is effective even when chemically negligible amounts of gallium are present.

In summary, it has been demonstrated that internal radiation derived from Ga^{72} inhibits the oxygen consumption of rat liver slices and that the degree of inhibition is related to the dose of radiation. The QO_2 of liver slices from control animals that received stable gallium was inhibited slightly during the two- to twelve-hour period after injection.

Repeated injections of stable gallium produced a liver QO_2 inhibition which was apparent ninety-six hours after the last injection. Repeated injections of Ga^{72} plus stable gallium produced no additional effect.

The glycogen content of livers from the stable and radioactive gallium rats was less than normal. This decrease persisted longer in the irradiated animals.

At the levels of radiation and gallium dosage used, there was no histologic evidence of liver damage during the period of QO_2 inhibition.

With repeated injections, leukopenia seemed to be the result of radiation, while the hemoglobin reduction was due to the effect of stable gallium. Gastrointestinal disturbances were produced by both stable and radioactive gallium, but appeared much sooner in the Ga^{72} animals.

IV. Toxicity of Gallium Citrate in Dogs and Rats

H. D. BRUNER, M.D., BETTY M. COOPER, M.D., and DONALD J. REHBOCK, M.D.¹

Studies on the toxicity of gallium citrate in dogs and rats were begun in October 1949 and continued during the following year. At that time, Dudley and his asso-

ciates (6, 10, 11, 17) had published the basic data which suggested that radioactive isotopes of gallium might segregate in osseous tissue in amount sufficient to be therapeutically useful against neoplasms of bone. By virtue of these data and per-

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sonal communication with Commander Dudley, it was possible to select the gallium citrate complex as the most biologically acceptable form of the metal which could be rapidly synthesized at the 500-mc. level (see Section II of this series).

Because this radiochemically prepared solution of gallium citrate contained extraneous material not present in solutions of the recrystallized pure complex, both forms were employed for these toxicity studies, but without noticeable difference in results. Only the intravenous route of administration was used, since radioactive gallium can be given to man solely by that route. Dudley and Levine (6) showed that gallium was not absorbed from the gut and only partially from subcutaneous and intramuscular deposits. Such unabsorbed radioactive material would produce severe radiation damage at the point of injection.

Following intravenous injection of the citrate complex, the animals exhibited generalized hyperirritability. If enough of the solution were given, they displayed opisthotonos and died acutely with respiratory paralysis. Presumably an acute hypocalcemia created by the citrate was responsible for death. Experiments on rats demonstrated that calcium given just prior to the gallium citrate prevented these acute deaths, and by trial and error it was established that the minimal effective prophylactic dose was approximately 2 mols of calcium ions per mol of citrate. This ratio suggests that much of the citrate was rapidly mobilized from the complex immediately following injection. Thus, deaths occurring within twenty-four hours after injection were not regarded as gallium-induced. In view of these observations the prophylactic administration of calcium as Calcium Gluconate Injection (U.S. P.) became an integral part of the administration of gallium citrate and was used in this 2:1 mol ratio preceding all injections of the citrate into man and animals.

EXPERIMENTAL METHODS

A total of 137 male rats of the Wistar-Carworth albino strain, weighing 200 to

275 gm., were used. After injection they were caged in pairs and given Checkers and water *ad libitum*. The injection procedure is important, since the apparent toxicity can be artificially increased by poor technic. The injections *via* the tail vein were made under light ether anesthesia in the belief that the rat suffered less trauma from the ether than from the struggle which otherwise takes place; also, such injections can be made with precision. The vein was entered with a 26-gauge needle attached by a short length of gum tubing to a tuberculin syringe filled with saline. While the saline was being injected slowly, the required amount of 10 per cent calcium gluconate was given by puncturing through the gum tubing; after the calcium had been washed in, the desired amount of gallium citrate was injected through the tubing, and it was then washed in with the remaining saline. This procedure was used in all rat experiments. It was especially advantageous when the gallium solutions were highly radioactive, in that the operators thus received a minimal amount of radiation. All injections were made *very slowly* and as aseptically as possible.

The dogs were healthy mongrels of both sexes weighing 5 to 14 kg. and caged individually. Commercial food was supplemented with bones. All injections were *via* the external saphenous or basilic veins and without anesthesia.

Four preparations of the citrate complex were used. The first was a radiochemical preparation described in Section II. This, the least pure form, is not taken through a crystallization stage. The second was a recrystallized sample obtained from Dudley containing 23.05 per cent Ga. The third and fourth were samples prepared from 98.5+ per cent purity metal, differing only in the number of recrystallizations and analyzed 22.5 per cent Ga. The latter three samples were dissolved in distilled water in amounts sufficient to give approximately an 8 per cent solution *after* adjustment to pH 7.2-7.4 with NaOH and passage through a No. 42 Whatman filter.

Filtration removed approximately 30 per cent of the gallium originally present and eliminated the initial opalescence of the solutions. The gallium concentration of the solution was then determined by direct analysis. In all cases, the doses have been calculated and expressed in terms of gallium element, not the gallium citrate complex.

By using normal red blood cells as osmometers, the filtered solutions were adjusted to approximately isosmotic concentrations with distilled water or NaCl solutions. In order to be able to administer the highest doses to rats, 1.5 times isosmotic solutions were prepared.

RESULTS

At a given dose level, at least two and usually three of the samples described above were used, but because there were no apparent differences between the preparations, the data have been combined.

1. *Toxicity of Single Doses in Rats:* No deaths due to gallium itself were observed in rats receiving doses up to 223 mg. Ga/kg. body weight. After higher doses, deaths did occur within twenty-four hours, but it is questionable if they were the result of toxicity of the metal. It proved impossible to administer larger amounts of gallium citrate without laying the data open to challenge on the ground of injecting too large a volume of solution, too hyperosmotic a solution, or unrealistic amounts of Ca and citrate ions. Thus, it is possible to state only that the 10-day LD 50 for rats was greater than 220 mg. Ga/kg. body weight.

For the first four to eight days after injection of the higher doses, the rats ate little, ceased to groom themselves, experienced mild diarrhea, and lost about 15 per cent of their body weight. By the twentieth day, however, they appeared normal, and by the thirtieth day had made up the initial weight loss. Histologic study of such recovered rats showed only mild cloudy swelling of the kidneys and increased hemosiderin in the spleen. Rats receiving lower doses were proportionally less affected. At the height of the reaction, the

sections showed mild to moderate renal tubular damage and lymphoid degeneration.

2. *Toxicity of Single Doses in Dogs:* Single injections of one of the above four samples of gallium citrate were given to 50 dogs in doses ranging from 10.6 to 47.0 mg./kg. body weight. The per cent surviving fifteen days later, computed by the cumulative method, was linearly related to the log of the dose. The 10, 50, and 90 per cent lethal dose values were 10.5, 18.2, and 41.1 mg./kg., respectively. Many of the animals living beyond fifteen days were severely debilitated and recovered very slowly; 3 were sacrificed when it became obvious that they would not recover.

Most dogs vomited soon after the injection, and all refused food and rapidly lost weight. Nearly every animal suffered from diarrhea; the stools were foul and blackish, and gave positive tests for blood. Those animals which survived exhibited the least anorexia and gastrointestinal upset. Debility and weakness progressed rapidly in those which died; death was preceded by coma. There were no outstanding characteristics in the clinical picture. Two females in early pregnancy aborted about twelve hours before death.

The urine samples always contained many red blood cells, granular and hyaline casts, and + to ++++ albumin according to the sulfosalicylic test, but no sugar. The blood urea nitrogen of animals dying after the fourth day ranged between 190 and 300 mg. per cent, but was not especially elevated in dogs dying twenty-four to seventy-two hours after injection.

In some dogs living more than fifteen days, the hemoglobin values were essentially unchanged, while in others the level was reduced to as much as 40 per cent of the control value. In general, the depression of hemoglobin was proportional to the degree of debility.

Rigor mortis appeared at once after death. At autopsy, the gastrointestinal tract contained only a semifluid chocolate material which gave a positive test for

blood, but gross bleeding points were not found. The kidneys were enlarged and pale. The lymph nodes all over the body were about three times normal size and firm. Bronchopneumonia was frequent and probably terminal.

Histologically, the renal damage resembled that of mercury poisoning. The tubular destruction ranged from cloudy swelling to severe necrosis with sloughing and blockade. Practically every section of the lymph nodes showed marked nuclear fragmentation and necrosis of the lymph

nodes, aplastic changes of the bone marrow, and mild to moderate signs of previous tubular damage. Nevertheless, according to chemical analyses, the liver, spleen, and kidney contained appreciable amounts of gallium (8 to 70 $\mu\text{gm./gm.}$ of wet weight). The bone usually retained more, while the lymph nodes had least. Presumably this metal is held in a biologically inert form.

In animals which died within forty-eight hours after administration of the

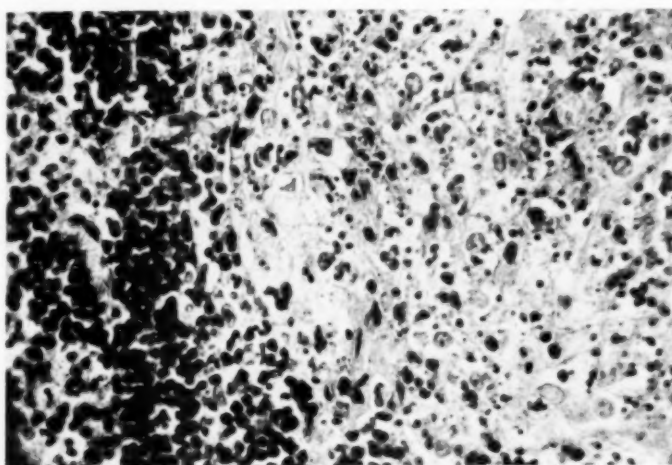


Fig. 9. A part of a follicle and germinal center of the lymph node of a dog dying seventy hours after receiving 35 mg./kg. of gallium citrate intravenously. The nuclear fragmentation and necrosis of the lymphoid elements are quite prominent. The polymorphonuclear infiltration is much greater in other sections, but is obvious here. Such nodes had a lower content of stable gallium metal than other tissues such as liver, which showed no damage. Similar nodes and sections have been forwarded to the Armed Forces Institute of Pathology. $\times 450$.

phoid elements, with polymorphonuclear infiltration; in some sections the latter was so intense as to suggest a purulent reaction. Figure 9 is a photomicrograph of a typical reaction. This histologic picture seems to have no counterpart so far as human pathology is concerned. The spleen showed a milder degree of this lymphoid reaction. The liver, pancreas, heart, intestine, and bone marrow were negative except for hyperemia; in the lung there was lobular pneumonia of recent origin.

Histologic sections of dogs surviving the acute phase were essentially negative ex-

cept for mild hyperplasia of the lymph nodes, aplastic changes of the bone marrow, and mild to moderate signs of previous tubular damage. Nevertheless, according to chemical analyses, the liver, spleen, and kidney contained appreciable amounts of gallium (8 to 70 $\mu\text{gm./gm.}$ of wet weight). The bone usually retained more, while the lymph nodes had least. Presumably this metal is held in a biologically inert form.

3. Toxicity of Repeated Small Doses in Dogs: Twenty-four dogs, in 3 groups of 8 each, received gallium citrate intravenously in doses of 5.0, 3.5, and 2.5 mg. of gallium per kilogram of original body weight twice a week until death. The immediate reaction by the gastrointestinal system to these smaller doses was compara-

tively mild, but the toxicity was otherwise accentuated. At the 5 mg./kg. dose level, 6 dogs died after the second dose (10 mg./kg. total) and the remaining 2 after the third. At the 3.6 mg./kg. level, 4 dogs died after the second dose (7.0 mg./kg. total) and 2 each after the third and fourth doses. At 2.5 mg./kg., 2 dogs each died after the third, fifth, seventh, and eighth doses. Dudley (18) has observed this summative effect at 5 mg./kg. on dogs and also on rabbits at the 10 mg./kg. level; it is therefore not a species peculiarity.

Anorexia, debilitation, and weight loss were of about the same degree as with the single large dose, but, being more spread out, were not quite so obvious. The first dose at these levels produced only a moderate illness, but the course became abruptly worse when the second dose was given. Granular casts and erythrocytes were present in large numbers in the urine following the second dose, and albumin was present in ++ to ++++ amounts. The hemoglobin and hematocrit levels decreased moderately in the longest surviving dogs, while the leukocyte count usually increased without particular change in the differential count.

At death, the blood urea nitrogen values ranged from 175 to 250 mg. per cent, but the histologic sections of the kidney suggested a milder degree of damage. The lymph-node reaction was qualitatively the same as in the single dose series, but distinctly more moderate in degree.

DISCUSSION

These data demonstrated such a widely different species sensitivity to intravenously administered gallium citrate that it was impossible to anticipate the probable toxicity in man. The cautious trials reported in Section VI of this series indicate that man is to be grouped with the dog but probably is more resistant. Man withstood the twice weekly doses of 2.5 mg./kg. or more much better than the dog and with total doses as large as 66.7, 70.2, and 111.6 mg./kg. spaced over six to fourteen weeks failed to show lymphadenopathy or urinary

changes indicative of renal damage. Nausea, vomiting, anorexia, and debility did occur in man, but in relation to the dose were not nearly as severe as in dogs. Various types of skin reactions, leukopenia, and/or hemorrhages signaled the discontinuance of therapy. The percentage of the dose which was excreted increased as the size of the dose increased, but in absolute terms increased amounts of the metal were laid down in the body when larger total doses were given. This point is discussed further in Section VII of this series (pp. 588-590).

Since a single dose of gallium given to man usually contained between 50 and 75 mc. of Ga^{72} , these toxic reactions cannot be ascribed solely to either the radiation from Ga^{72} or the metal carrier. In fact, it is not unlikely that the two forms of injury complement one another.

Dudley, Henry, and Lindsley (19) compared the toxicity of subcutaneously administered gallium citrate in five species. The ten-day LD 50 values were: mouse, 600 mg. Ga/kg.; rat, 110 mg./kg.; rabbit, 45 mg./kg.; dog and goat, less than 15 mg./kg. In young rats weighing 50 to 100 gm., a value of 230 mg./kg. was found. The LD 50 for intravenous administration in 10 dogs was in the neighborhood of 15 to 20 mg./kg., equaling that reported above. Experiments with gallium lactate (6) demonstrate, however, that the intravenous route approximately doubles the apparent toxicity of the metal.

The toxic syndrome described by Dudley *et al.* (19) in rabbits which had received gallium lactate or citrate subcutaneously agrees in essentials with that observed in dogs in these experiments. In both species the immediate cause of death was uremia secondary to acute damage to the renal tubules. The detailed biochemical studies of Dudley and his associates, on rabbits, supplement the above histologic data on dogs. It should be pointed out, however, that the data presently available do not specify the manner by which gallium intrinsically damages cells. The deaths which occurred twenty-four to forty-eight

hours after injection were without outstanding histologic lesions, so that the uremic syndrome is perhaps to be regarded as one of the effects of the metal that is particularly prone to kill because of its relation to excretion. Other points for which no explanation can be offered are: (a) the lymph-node reaction, seen chiefly in the dog; (b) the large species variability in toxicity; (c) the excessive effects of repeated small doses of the metal.

The general toxicity experiments can be summarized as follows:

1. The ten-day lethal dose for rats following intravenous administration of gallium citrate was greater than 220 mg. Ga/kg. body weight. Larger amounts could not be given for chemical and physiological reasons.

2. The fifteen-day LD 50 for dogs after intravenous administration of the same

preparations was 18.2 mg. Ga/kg. The data plotted as per cent surviving *vs.* log of dose fell very close to a straight line.

3. Dogs given fractional doses intravenously twice a week succumbed after smaller total doses of metal. The toxicity seemed to be accentuated.

4. The clinical syndrome resembled an acute debilitating disease involving particularly the gastrointestinal tract and terminating by uremia. Histologically, the kidneys were chiefly involved as in mercury poisoning. In dogs, a novel feature was an acute lymphadenitis with polymorphonuclear reaction to lymphoid degeneration. These lesions were repaired in animals which survived.

5. The large species differences made useless further work for the purpose of estimating the probable toxicity of the metal for man.

V. Distribution Studies on Gallium⁷² in Rats

H. D. BRUNER, M.D., JESSE D. PERKINSON, JR., PH.D., E. R. KING, M.D.,⁷ GOULD A. ANDREWS, M.D., JOE B. NASH, PH.D.,⁸ and MARSHALL BRUCER, M.D.

The following series of experiments on rats was carried out preliminary to the use of Ga⁷² for the treatment of osteogenic and related neoplasms in man. The reports by Dudley and his associates (6, 10, 11, 17, 20) established that the metal had a definite affinity for bone and actively metabolizing osseous tissues but, because of the tediousness of the chemical method of assay, their data were limited in scope and not adequate as a basis for designing clinical procedures. Subsequently, and concurrently with the experiments reported here, they used the Ga⁷² tracer method to obtain additional data (19, 21-23), which in general agree with those below.

These experiments were planned as prototypes of the clinical studies. Since the metal had never been administered to

man, these animal experiments were the sole guide to what might be observed clinically. It was recognized that quantitative data from the rat could not be transferred directly to human beings but that the general biological relations obtained in the rat should hold in man. The objections which might be raised to using the rat for this purpose would also apply to any other species.

The various compounds of gallium used in these experiments were always injected intravenously. This is the only route suitable for clinical administration of the radioactive isotope, since incomplete absorption from subcutaneous or intramuscular deposits would lead to local necrosis; the metal is not absorbed from the gastrointestinal tract (6).

In these experiments the animals were sacrificed at regular intervals to secure a complete sequence of the changing concentrations of metal and isotope in the various tissues. A total of thirty-four tis-

⁷ Commander, MC, USN. The opinions or conclusions in this report are those of the authors and are not to be construed as necessarily reflecting the views or endorsement of the Navy Department.

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sues or parts of organs and the excreta were analyzed. Special attention was given to small but vital structures such as the adrenals, pituitary, and eye, where a comparatively low concentration of isotope might result in a disproportionate amount of overall dysfunction. Also, there was always the possibility that the metal might localize selectively in one of these tissues.

Whether Ga^{72} will selectively localize in human osteogenic neoplasms cannot be answered by animal experiments. Even if there were a comparable experimental osteogenic tumor, the final answer would have to come from observations on patients. On the other hand, the experiments below supply information which ought not to come from observations on man or cannot on account of the sporadic and uncertain nature of autopsy material.

EXPERIMENTAL PROCEDURES

The rats were randomized healthy adult males of the Carworth-Wistar strain, weighing 240 ± 30 gm. All injections were given *via* a tail vein while the rat was under light ether anesthesia lasting less than ten minutes. The possible trauma of anesthesia was considered preferable to the struggle or application of force otherwise necessary.

The following procedure was used for intravenous injections: A tuberculin syringe was connected to a 26-gauge needle by a very short piece of intravenous gum rubber tubing and filled with sterile saline. When the needle was in the vein and the saline flowing in very slowly, the solution of isotope in another syringe was added to the inflowing saline by puncturing the connecting tubing. When calcium gluconate was used, it was injected prior to the isotope and washed in with saline. The injection was made very slowly; three to five minutes were required to administer the total volume of 1.5 to 2.0 ml. Because the solution of isotope was not sterile and no attempt was made to sterilize the rats' tails, the procedure should be termed "clean" rather than "sterile"; there was never any evidence of systemic infection in

these or other similarly injected animals.

After injection, the rats lived in a special metabolism cage from which the feces and urine could be collected without cross-contamination (24). They were supplied with Checkers and water *ad libitum*. At specified intervals, the rats were slowly viviperfused with 150 to 200 ml. of heparinized saline under light pentobarbital anesthesia. Removal of the blood was necessary because at six and twelve hours after injection the concentration of Ga^{72} was higher in blood than in many tissues, while later it was lower. The tissues to be analyzed, either the whole organ or portions of it, were weighed, transferred to volumetric flasks, dissolved in concentrated HNO_3 with the aid of gentle heat, and made to volume. What remained of the carcass was also dissolved and treated like the samples. The total dose of Ga^{72} was obtained from the sum of the samples and the carcass rather than the supposedly injected dose, which was found to be highly unreliable, particularly when small volumes were given.

The animals were dissected in a standard manner, and in the case of skin, muscle, salivary glands, lymph nodes, etc., the same regions or parts were taken. The right femur was dissected out, freed of skeletal muscle, and the ends of the femur separated from the shaft by oblique tension on the epiphyseal lines. The marrow was not removed from any bone sample. The four incisor teeth were extracted together with their pulpy roots; the latter, according to autoradiographs, were the most active areas of the entire animal. The activity of the skeleton was computed as 7.06 per cent of the body weight times the activity of the femur, which was considered the average for bone (25).

The counting system for Ga^{72} consisted of a 30 mg./sq. cm. carbon cathode glass tube mounted horizontally in a horizontal lead shield. A plastic carriage holding the sample in a 5-cm. machine-made Petri dish moved on a track to a fixed point beneath the tube. The Petri dishes held 10 cm. of the liquid digest and, where possible,

a 10 ml. volumetric was used for digesting, so that the transfer consisted merely of carefully pouring its contents into the dish.

The efficiency of counting, based on millicuriage calculated from electroscope measurements related to a NBS radium needle (Section I), varied between 1.55 and 1.80 per cent with different tubes. The background counting rates ranged from 25 to 34 counts per minute. The samples were counted to give standard deviations of ± 2 per cent or less except where the net counting rate was only 1 or 2 times background where ± 5 per cent or less was accepted.

Three different representative chemical forms of gallium were examined as follows:

(a) GaCl_3 , which is an ionized soluble salt at pH 2.0-2.2 and below; above pH 2.2 an insoluble hydroxide forms. The Ga^{+++} ion reacts with nearly every anion in the blood, including proteinate to form insoluble precipitates.

(b) Gallium alizarinate, which is an insoluble but highly dispersed chelate or lake at pH 7.4. The exact composition was indefinite and it was prepared in small batches as needed.

(c) Gallium citrate, which is a stable, soluble complex at pH 7.4. It reacts with proteins very slowly, if at all.

Two preparations of the citrate complex were used, the details of which are given in Section II: a very pure complex produced on an ion exchange resin surface having 5 mols of citrate per mol of Ga^{+++} and a less purified but rapidly prepared complex having ~ 1.2 mols of citrate per mol of Ga^{+++} . This form is identified by the term "radiochemical." It was used routinely for the patients. Apparently the citrate ion was rapidly mobilized after injection because the animals went into hypocalcemic tetany and died unless treated prophylactically with Ca^{++} as Calcium Gluconate Injection (U.S.P.). By trial and error, the dose of Ca^{++} was found to be 2 mols per mol of citrate.

Except for one series, only enough radioactivity was injected to give suitable counting rates on the intended day of sacrifice.

This resulted in a corresponding variation in dose of carrier, *i.e.*, inert $\text{Ga}^{69,71}$. This was not a constant variation, since the specific activity of the gallium was not constant. The maximum specific activity was slightly over 1 mc./5 mg., but usually it was lower due to physical decay during preparation of the solution. To minimize this "batch effect" and to control variations arising from changes in weather, food intake, health of the colony, etc., two rats intended for each sacrifice time over the whole experiment were injected from each freshly prepared batch.

RESULTS

The data from each of the five series of experiments were identical in type and are presented in similar form. In the tables the numbers of rats injected for sacrifice at each time interval and the dose ranges in millicuries per kilogram are shown at the top of each column. Below are the average cumulative percentages of the total dose which were retained or excreted, and the distribution of the excreted fraction between the urine and feces.

The three most useful ways of presenting the distribution data are given in the two lower sections of each table and the companion figure. The *total organ content in per cent of retained dose* indicates the distribution of gallium present in the animal but without reference to the actual amount present. This is useful in judging relative shifts of gallium content on an organ level. Multiplying the retention data by these percentages gives the values used to construct the figures. For brevity, only the organs showing an important uptake of gallium are shown. The skin and skeletal muscle, which comprise about 70 to 75 per cent of the rat's weight, contribute most of the activity lumped under "Remainder."

The *differential absorption ratio*, the DAR of Marinelli (3), is defined as

$$\frac{\text{Activity per gram of tissue}}{\text{Total retained activity/body weight}}$$

By normalizing the gallium content in a tissue relative to dose, excretion, and ani-

TABLE VII: DISTRIBUTION OF Ga^{72} IN MALE RATS SACRIFICED AT INTERVALS AFTER INTRAVENOUS INJECTION OF Ga^{72} -LABELED $GaCl_3$ AT pH 2.0-2.2

(Each value is the average of the number of rats at the top of the column)

Number of rats Time sacrificed (hr.)	5 6	5 12	4 24	5 48	5 96
Dose					
mg. Ga^{+++} /kg.	0.7-2.6	0.8-6.8	0.8-3.6	1.5-8.0	2.4-8.0
mc./kg.	0.02-0.56	0.02-1.35	0.16-0.80	0.41-2.94	0.47-1.62
Per cent of original dose retained	75.8	61.7	59.8	40.9	32.9
Per cent of original dose excreted	24.2	38.3	40.2	60.1	67.1
Fraction in:					
Urine (%)	99.7	97.1	91.3	93.0	88.9
Feces (%)	0.3	2.9	8.7	7.0	11.1
Total organ content in per cent of retained dose					
Blood plasma*	8.9	3.1	3.1	1.1	0.7
Blood cells	0.7	0.5	0.4	0.1	Negligible
Liver	27.9	19.4	23.2	11.8	19.6
Spleen	0.6	1.0	1.2	0.8	1.4
Kidney	1.4	3.0	2.4	5.9	5.7
Skeleton†	29.4	38.2	30.7	46.2	44.7
Remainder	31.2	34.7	39.0	34.1	27.9
Differential absorption ratio					
Blood plasma	2.6	1.5	0.9	0.3	0.2
Blood cells	0.2	0.2	0.1	Negligible	Negligible
Liver	7.4	5.0	4.9	3.0	3.8
Spleen	2.6	2.8	5.0	2.9	5.1
Kidney	1.6	3.0	2.7	6.1	5.6
Femur	4.2	5.4	5.6	6.4	6.8
Teeth	3.0	4.9	4.6	6.8	12.3
Skeletal muscle	0.2	0.1	0.3	0.2	0.1
Thymus	0.5	0.3	0.4	0.3	0.5
Heart	0.2	0.2	0.2	0.1	0.2
Lung	0.6	0.5	0.6	0.4	0.6
Skin	0.8	0.7	1.1	0.3	0.4

* Plasma and blood cells computed as 7.5 per cent of the body weight times the determined hematocrit.

† Skeleton computed as 7.06 per cent of the body weight times the activity per gram of femur (11).

mal size, the DAR greatly facilitates inter-comparison of animals within a group, as well as intergroup and interseries comparisons. Also, because the roentgen is defined in terms of volume, this normalized activity per gram bears a direct relation to the relative dose of radiation received by tissues except in the case of bone.

Each value in the tables is the average of the number of rats at the top of the respective column. In general, these averages truly represent the central tendency, but occasionally a single, or rarely two, high or low values of unexplained origin threw the average out of line. The standard deviations of these means adjusted for small numbers were nearly always within 30 per cent of the mean; the exceptions were within 50 per cent. The mean and median values nearly always coincided. The use of larger numbers of rats per group would

have given smaller variances, but the basic information secured by averaging 4 to 7 rats would not have been essentially improved by doubling the number of animals.

1. The Distribution of $GaCl_3$

In interpreting these data, it should be kept in mind that gallium existed as Ga^{+++} in this preparation. On entering the vein, it probably reacted with several blood constituents to form precipitates, but there is no information on what these reactions are, or on the subsequent history of the reaction products. Four batches of $GaCl_3$ were prepared in physiological saline at pH 2.0 to 2.2; they contained 2 to 4 mg. of Ga^{+++} per milliliter.

The excretion data in Table VII show that most of the excretion took place during the first twenty-four hours after injection and that the urinary system carried nearly

all of the load. Thereafter, the urinary and fecal excretion were about equal. The appearance of Ga⁷² in the six-hour fecal samples suggests that the metal was excreted by the mucosa of the large intestine. In separate acute experiments,⁹ Ga⁷² appeared in hepatic duct bile within three to five minutes after intravenous injection of GaCl₃ or gallium citrate. The concentration of Ga⁷² in the bile paralleled the concentration in the plasma, but was some five times greater. The progression of maximal Ga⁷² activity through the gastrointestinal tract, which was analyzed in five sections, indicates that the duodenal region was the source of the most of the activity in the feces. Because the pancreas and the wall of the gut showed low relative concentrations of Ga⁷², the liver was assumed to be the source of the activity. No part of the genitourinary tract other than the kidneys showed appreciable concentrations of Ga⁷².

The "biological half-life" (3) was twenty-one hours. The animals which received the highest doses of gallium metal excreted a larger fraction of the dose.

Table VII shows that the liver had the highest relative concentration initially; subsequently it decreased more or less in parallel with the plasma concentration. The differential uptakes of the spleen and kidneys at first were relatively low, but increased with time. The femur (as representative bone) had the highest differential uptake of the twenty-four-hour samples but still only slightly higher than the next three tissues. The incisor teeth showed the highest absorption ratios; most of the activity was in the pulpy roots. The remaining twenty-nine tissues, including skin, muscle, glandular, lymphoid, and nervous tissue, some of which are listed in Table VII, gave no evidence of segregation.

Figure 10 demonstrates that the liver and plasma rapidly lost their initial content, while the spleen, kidney, and skeleton retained essentially the Ga⁷² which they had at twenty-four hours. Therefore, the increased differential absorption ratios of

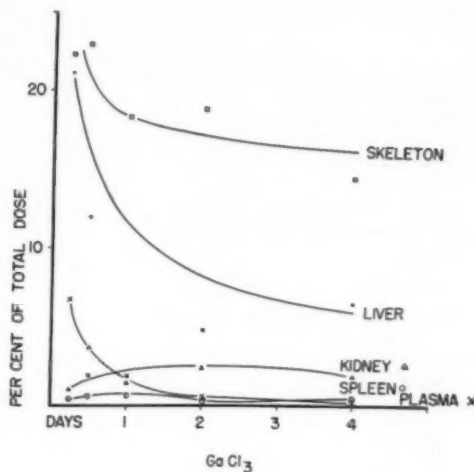


Fig. 10. The percentages of the original total dose of Ga⁷² retained by the organs showing the highest differential absorption ratios. The metal was injected intravenously as GaCl₃ at pH 2.0 diluted with physiological saline solution.

the bone, spleen, and kidney were the result not of a continuing uptake of Ga⁷², but of the loss of Ga⁷² from the liver and soft tissues such as skin and skeletal muscle.

Comment: Because 68.8 per cent of the initial number of radioactive Ga⁷² atoms decay during the first twenty-four hours following injection, that period is relatively the most important with respect to radiation dose to tissues. Thus, during the first twenty-four hours, the liver received more radiation per gram of tissue than did bone; subsequently, the bone received a higher dose than the liver or other tissues, but the difference after twenty-four hours was comparatively minor and did not compensate for the larger difference during the first twenty-four hours. In any case, the total dose to the bone over the ninety-six hour period (6.7 half-lives) was of the same order as that to the liver and was far short of the five- to ten-fold difference that would be the minimum for therapeutic purposes. In addition, the liver and viscera were subjected to a cross-fire of γ radiation from the Ga⁷² distributed over the trunk; the long bones of the limbs and the bones of the head escape much of this cross-fire (*c.f.* Marinelli, Quimby and Hine, 3).

⁹ Performed by Dr. J. W. Archdeacon.

TABLE VIII: DISTRIBUTION OF Ga^{72} IN MALE RATS SACRIFICED AT INTERVALS AFTER INTRAVENOUS INJECTION OF Ga^{72} ALIZARINATE AT pH 7.4

(Each value is the average of the number of rats at the top of the column)

Number of rats Time sacrificed (hr.)	4 6	6 12	6 24	4 48	4 72	6 96
Dose mg. Ga^{+++} /kg. mc./kg.	0.2-0.4 0.05-0.09	0.3-0.4 0.06-0.10	0.2-0.5 0.04-0.11	0.3-1.2 0.04-0.23	0.4-1.7 0.07-0.31	0.7-1.2 0.17-0.28
Per cent of original dose retained	88.2	85.6	58.8	65.9	60.7	58.2
Per cent of original dose excreted	11.8	14.3	41.2	34.1	39.3	41.8
Fraction in:						
Urine (%)	97.8	74.3	76.8	77.3	69.4	
Feces (%)	2.2	25.7	23.2	22.7	30.6	
Total organ content in per cent of retained dose						
Blood plasma*	0.6	0.4	1.3	0.3	0.2	Negligible
Blood cells	0.1	0.2	0.2	0.1	0.2	Negligible
Liver	55.1	51.3	28.8	50.5	46.8	48.3
Spleen	4.0	1.7	4.9	5.5	4.8	7.6
Kidney	1.5	4.4	6.9	2.4	2.0	0.7
Skeleton†	14.7	18.6	51.7	24.1	27.7	20.4
Remainder	24.0	23.4	6.2	17.1	19.4	23.0
Differential absorption ratios						
Blood plasma	1.0	1.1	1.9	0.3	0.2	Negligible
Blood cells	0.3	0.5	0.3	0.1	0.2	Negligible
Liver	14.4	14.4	7.7	13.7	11.3	13.0
Spleen	7.3	4.4	15.3	16.1	15.5	18.6
Kidney	2.0	5.9	9.5	3.5	2.8	1.0
Femur	1.9	2.6	7.2	3.4	3.8	2.9
Shaft	2.2	2.5	7.2	3.7	3.7	3.3
Ends	1.5	2.7	7.2	3.0	2.9	2.4
Heart	0.4	0.3	0.4	0.2	0.2	0.2

* and † See footnotes to Table VII.

In summary, gallium given intravenously as $GaCl_3$ was not distributed differentially to any one tissue rapidly enough or to a sufficient degree to suggest that this form of gallium ought to be administered therapeutically in man. This form of gallium, soluble at pH 2.0-2.2, or below, is pharmacologically undesirable for intravenous purposes because it may result in embolism and local irritation.

2. The Distribution of Gallium Alizarinate¹⁰

The high differential absorption ratios of the spleen and liver in the $GaCl_3$ experiments suggested that particulates had formed which the reticulo-endothelial tissue of these organs phagocytized. Thus, these differentials were the result of physicochemical properties which resulted in a non-specific distribution.

To test this possibility, gallium was pre-

pared in a soluble particulate form, a chelate or lake with alizarine. A 10 per cent solution of alizarine red in 4 *N* NH_4OH was added to a solution of $GaCl_3$; on neutralizing this with 1.66 *N* acetic acid, a precipitate formed which was washed three times, then suspended in water and put into solution by use of $NaHCO_3$ and heat. The lake was freshly prepared for each series of rats injected.

The twenty-four-hour data in Table VIII were completely out of line due to anomalous values from 2 of the 6 rats sacrificed at that time. The average of the other 4 rats would have fitted into the sequence but the values on these 2 animals were included since 6 other rats which received the same preparation for sacrifice at later periods did not show anomalous values.

The total excretion of Ga^{72} and its distribution between the urine and feces (Table VIII) were distinctly different than after injection of $GaCl_3$ or gallium citrate. The excretion was comparatively small

¹⁰ These experiments were made by Joe B. Nash.

during the first twelve hours after injection, and the total excretion was only about two-thirds of that in the other experiments. To anticipate the findings in later experiments, this was not the result of low doses of carrier metal. The high percentage of Ga⁷² in the feces was a result of the decreased urinary excretion, because the absolute amount in the feces was similar to that in the other experiments. No value can be given for the biological half-life, but it was more than four days, and by graphical extrapolation ~ 10 days.

Immediately after injection, the liver showed the highest differential absorption (Table VIII). The spleen was about half as active, and bone about one-seventh as active. As the experiment proceeded, the spleen became the most active tissue, passing the liver between twenty-four and forty-eight hours. At no time was bone more than one-fifth as active as the liver or spleen. The liver contained nearly half of the Ga⁷² which was retained, and the skeleton 20 to 25 per cent. In terms of the original dose (Fig. 11), the liver lost about 40 per cent of the Ga⁷² which it had initially, while the spleen and bone retained their initial uptake or perhaps added to it. The plasma was nearly cleared of Ga⁷² by six hours, in contrast to the forty-eight-hour exponential decrease following administration of the other two gallium compounds.

Comment: The rapid disappearance of the injected material combined with the high differential uptakes of the spleen and liver point to removal of the particulate matter by phagocytic action of the reticulo-endothelial cells. On the other hand, the presence of Ga⁷² in tissues such as heart and red cells (Table VIII) indicates that some of the gallium was loosely bound to the alizarine or possibly was liberated by action of the body metabolic processes. In the face of this contradiction, these experiments cannot be regarded as typifying the distribution that would result if an insoluble, inert colloid formed when the gallium was injected intravenously. It is safe to conclude, however, that gallium in par-

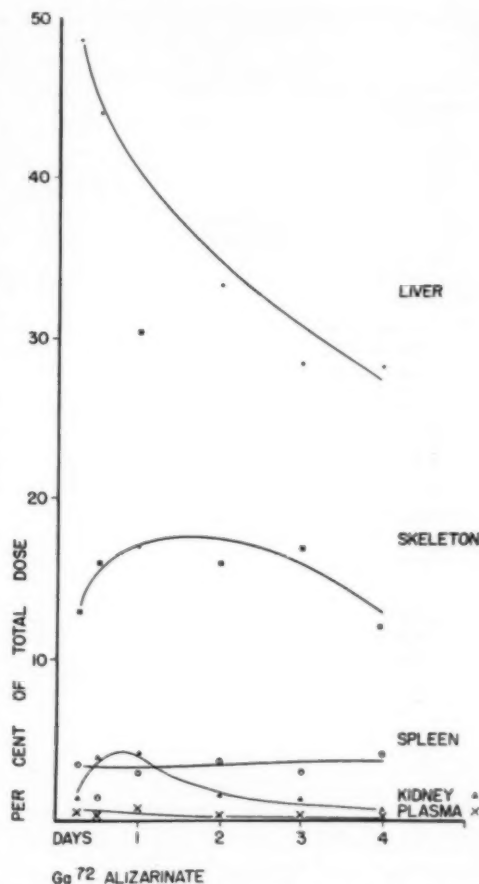


Fig. 11. The percentages of the total dose of Ga⁷² retained by the organs showing the highest differential absorption ratios. The gallium was injected as the alizarinate at pH 7.4 diluted with physiological saline solution.

ticulate form does not show a localization favoring bone. It should be injected in a form which will minimize *in vivo* precipitation.

3. The Distribution of Gallium Citrate: Ion Exchange Preparation

Work by Dudley (8) indicated that the citrate complex was preferable for intravenous use. A number of other organic and inorganic compounds of gallium were examined chemically (Section II), but none was found more acceptable than the citrate. Manufacture of the pure citrate using Ga⁷² was out of the question because of handling

TABLE IX: DISTRIBUTION OF Ga^{72} IN MALE RATS SACRIFICED AT INTERVALS AFTER INTRAVENOUS INJECTION OF Ga^{72} CITRATE (pH 7.4) PREPARED ON AN ION EXCHANGE COLUMN

(Each value is the average of the number of rats at the top of the column)

Number of rats Time sacrificed (hr.)	4 12	4 24	4 48	4 72	4 96
Dose					
mg. Ga^{+++} /kg.	0.2-0.6	0.4-1.4	1.4-2.3	6.0-6.5	6.0-6.9
mc./kg.	0.01-0.02	0.02-0.06	0.06-0.10	0.25-0.27	0.25-0.29
Per cent of original dose retained	74.4	72.8	46.5	27.7	20.5
Per cent of original dose excreted	25.6	27.2	53.5	72.3	79.5
Fraction in:					
Urine (%)	88.6	94.8	91.5	90.8	90.6
Feces (%)	11.4	5.2	8.5	9.2	9.4
Total organ content in per cent of retained dose					
Blood plasma*	8.8	4.2	1.4	1.1	0.3
Blood cells	0.4	0.5	0.4	0.5	Negligible
Liver	10.8	11.5	10.5	4.0	5.8
Spleen	1.1	1.2	1.8	0.5	0.6
Kidney	1.2	1.3	1.4	1.1	1.5
Skeleton†	29.3	27.4	53.6	58.5	67.8
Remainder	48.4	53.9	30.9	34.3	24.0
Differential absorption ratios					
Blood plasma	2.5	1.2	0.4	0.3	0.1
Blood cells	0.1	0.1	0.1	0.2	Negligible
Liver	2.8	3.2	2.7	1.0	1.4
Spleen	4.0	5.2	3.9	2.0	2.6
Kidney	1.5	1.8	1.9	1.6	2.3
Femur	4.3	3.9	8.1	8.7	9.8
Shaft	3.7	3.4	6.1	8.9	9.3
Ends	5.2	4.6	8.9	8.5	10.1
Teeth	3.4	4.3	8.1	9.7	11.6
Calvarium	2.4	2.7	4.4	5.0	7.3
Lung	0.8	0.8	0.7	0.7	0.8
Heart	0.4	0.3	0.3	0.1	0.2

* and † See footnotes to Table VII.

problems and the twenty-four hours necessary for the synthesis. An alternate method of quickly synthesizing a pure citrate complex was developed which made use of the surface properties of an ion exchange resin (9). The material so prepared was never administered to patients, because, as was learned here, the citrate can be rapidly mobilized from the complex and is potentially lethal. The best preparation had a ratio of 5 mols of citrate per mol of gallium. Accordingly Ca^{++} was administered prophylactically in the ratio of 2 mols of Ca^{++} per mol of citrate.

Results: The data have been summarized in Table IX and Figure 12. As with $GaCl_3$, excretion of Ga^{72} proceeded rapidly during the first twenty-four hours after injection and tapered off exponentially. The total excretion was 80 per cent of the injected dose, in contrast to 60 per cent for $GaCl_3$. Most of the excretion took

place by way of the kidney, and it continued for seventy-two hours instead of being confined chiefly to the first twenty-four hours after injection. The fecal excretion was greatest between twenty-four and forty-eight hours.

The liver, spleen and bone had about the same differential absorption ratios twelve hours after injection (Table IX); at ninety-six hours, the differential absorption ratio of the femur was seven times that of the liver and four times that of the spleen. This shift in favor of the bone began to take place between twenty-four and forty-eight hours. Figure 12 shows that the differential favoring bone occurred by virtue of the bone losing relatively less of its initial uptake than did the liver, plasma, kidney, and spleen. In this series of experiments the ends of the bone were somewhat more active than the shaft; in the other experiments the shaft was definitely more

active. The calvarium, a typical flat bone, was less active than the femur, but the changes of differential absorption ratio paralleled those of the femur. The mandible, not shown in Table IX, had a differential absorption ratio about midway between the femur and calvarium.

Comment: In terms of radiation dose, the bone did not receive a differential which would be therapeutically useful, since the differential absorption ratio in favor of bone occurred after 70 per cent of the radiation had been expended. Nevertheless, this was an improvement over the GaCl_3 distribution.

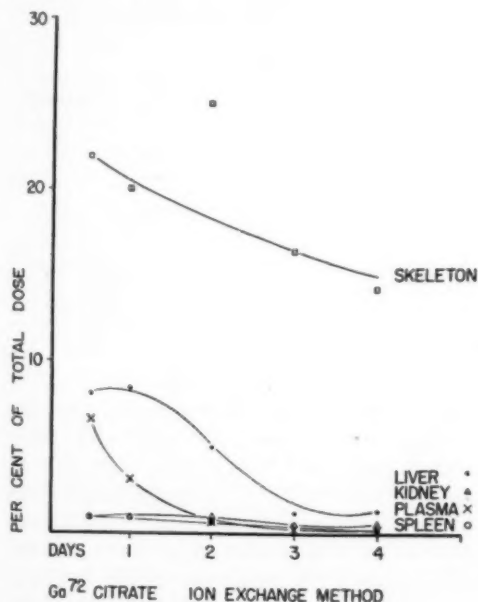


Fig. 12. The percentages of the total dose of Ga^{72} retained by the organs following intravenous injection of the gallium citrate complex at pH 7.4 and preceded by calcium gluconate. The citrate was prepared on an ion exchange column (9) and had 5 mols of citrate per mol of gallium.

4. Distribution of Gallium Citrate; "Radiochemical" Preparation (Variable Dose)

The "radiochemical" preparation of gallium citrate contained approximately 1.2 mols of citrate per mol of gallium. It was impure in that NO_3^- , Cl^- , and Na^+ , introduced during the preparation, were not re-

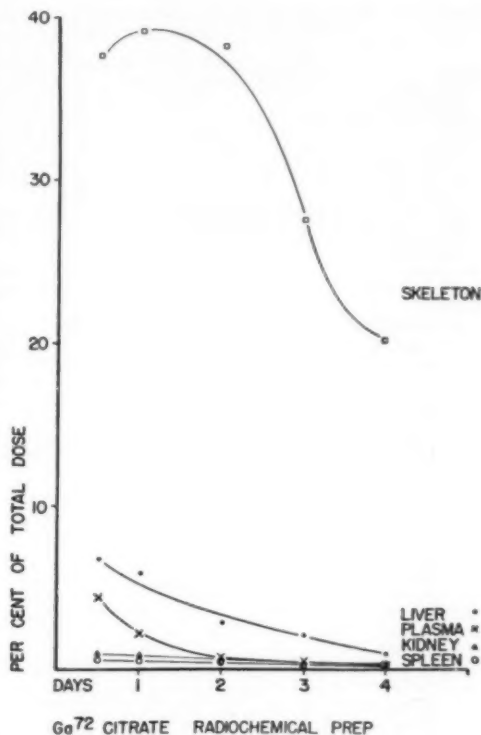


Fig. 13. The percentages of the total dose of Ga^{72} retained by the organs following intravenous injection of the gallium citrate complex prepared by the "radiochemical" method described in Section II. The solution contained 1.2 mols of citrate per mol of gallium at pH 7.4. The dose of carrier gallium increased with the length of time before sacrifice.

moved and the citrate was not separated or crystallized. On the other hand, this synthesis plus an assay of radioactivity required less than ninety minutes. Ca^{++} was employed in the usual proportion of 2 mols per mol of citrate.

Results: As with the ion exchange preparation, the most rapid excretion occurred during the first twenty-four hours after injection and continued at a reduced rate over the next two days; 77 per cent of the initial dose was excreted in ninety-six hours (Table X). The urine was the chief route of excretion, during the early observations, but after a longer interval the urinary and fecal loads were about equal. The biological half-life was 20.6 hours.

In these experiments, where there was a

TABLE X: DISTRIBUTION OF Ga^{72} IN MALE RATS SACRIFICED AT INTERVALS AFTER INTRAVENOUS INJECTION OF Ga^{72} CITRATE (pH 7.4) USING VARIABLE DOSES OF THE "RADIOCHEMICAL" PREPARATION
(Each value is the average of the number of rats at the top of the column)

Number of rats Time sacrificed (hr.)	5 12	5 24	5 48	5 72	5 96
Dose					
mg. Ga^{+++} /kg.	0.5	0.5	2.1	6.8	26.0
mc./kg.	0.08	0.11	0.45	1.4	5.3
Per cent of original dose retained	65.0	59.4	47.5	37.5	23.4
Per cent of original dose excreted	35.0	40.6	52.5	62.5	76.6
Fraction in:					
Urine (%)	85.3	94.2	91.7	90.3	89.7
Feces (%)	14.7	5.8	8.3	9.7	10.3
Total organ content in per cent of retained dose					
Blood plasma*	6.8	3.6	1.0	0.6	0.5
Blood cells	3.9	3.1	2.0	1.1	0.1
Liver	10.4	9.8	5.9	5.3	3.9
Spleen	1.0	1.1	0.8	0.4	0.3
Kidney	1.3	1.3	1.3	0.9	0.8
Heart	0.1	0.1	0.1	0.1	Negligible
Skeleton†	58.0	65.9	80.6	73.8	89.2
Remainder	20.5	15.1	8.3	17.8	6.2
Differential absorption ratios					
Blood plasma	1.5	0.8	0.3	0.2	0.1
Blood cells	0.1	0.1	0.1	0.1	Negligible
Liver	2.1	2.1	1.3	1.1	0.9
Spleen	2.1	2.2	1.7	1.2	1.0
Kidney	1.7	1.5	1.4	0.9	0.9
Femur	8.1	9.3	11.4	11.3	14.1
Shaft	10.2	11.7	13.5	13.6	18.2
Ends	6.3	7.4	9.5	8.8	10.5
Teeth	2.6	2.7	5.1	5.6	6.8
Calvarium	3.5	4.4	6.1	5.6	8.7
Heart	0.3	0.2	0.2	0.1	0.1
Lung	0.7	0.5	0.3	0.4	0.2
Lymph nodes	0.6	0.7	0.7	0.3	0.3

* and † See footnotes to Table VII.

wide variation in the amount of carrier gallium injected, it became clear that the percentage of the total dose which was excreted was related to the size of the dose of metal: The higher the dose, the larger the percentage excreted; however, in absolute milligrams of gallium, more of the metal was retained after the larger doses. This effect is further discussed below.

The differential absorption ratio of the femur twelve hours after injection was four times higher than that of the next highest tissues, the spleen and the liver (Table X). This difference increased as the experiment proceeded; at forty-eight, seventy-two, and ninety-six hours the bone was 6.7, 9.5, and 14 times more active than the next highest tissue. As shown in Figure 13, the soft tissues retained only one-fourth or less of their initial content, while the bone retained about half.

The shaft of the femur was not purely cortical bone, since the epiphyseal line, which has a very high uptake according to autoradiograms (17) (Section IX), remained attached to the shaft. The marrow, which was not removed from the shaft, could hardly be the source of the activity, since the trabecular bone of the ends of the femur was still more cellular, but less active. The calvarium, composed of tabular bone and some marrow, was about half as active as the femur.

Comment: This series, in contrast to the preceding, showed differential absorption ratios which would support the use of Ga^{72} to irradiate osteogenic neoplasms in man. The data indicate that the bone received four to five times as much radiation as the liver and possibly fifteen to twenty times as much as the soft tissues during the first twenty-four hours following injection.

Subsequently, the differential in favor of bone was still larger, but only 30 per cent of the activity remained. However, two sources of generalized radiation not immediately apparent from the tables tend to reduce the differential. One is the Ga⁷² circulating in the plasma and red cells; this results in whole-body irradiation, but it appears to be negligible. The other is the activity stored in the urinary and gastrointestinal tracts prior to excretion; this is significant in view of the ~ 50 per cent of the dose which was excreted during the first day.

It is suggested tentatively that gallium citrate manufactured by this particular method has a special affinity for bone and little affinity for the viscera. The relatively low uptake by the spleen and liver probably is associated with the non-particulate nature of the complex, and later with slow liberation of the metallic ions. These observations would seem not to be sporadic experimental artifacts, since four different batches of the radiochemical preparation were used.

5. Relation of Size of Dose of Gallium to Amount of Gallium Excreted

The data collected in Table XI were taken from sections 1, 3, and 4 above, to-

TABLE XI: EXCRETION OF Ga⁷² IN THE URINE OF RATS IN PER CENT OF THE INJECTED DOSE DURING THE FIRST TWENTY-FOUR HOURS

	Dose of Ga ⁺⁺⁺ in mg./kg.	Per cent Excreted	Urine/feces*
GaCl ₃ (Result A)	0.8-3.6	36.7	10.5
	1.5-8.0	53.8	22.0
	2.4-8.0	52.3	19.4
Ion exchange gallium citrate (Result C)	0.4-1.4	22.8	4.9
	1.4-2.3	44.8	14.4
	6.0-6.5	67.4	43.2
	6.0-6.9	74.2	32.3
"Radiochemical" gallium citrate (Result D)	0.5	35.0	6.3
	2.1	44.9	11.7
	6.8	54.9	20.2
	26.0	71.7	60.7
Carrier-free gallium citrate (Section X)	Less than 10 ⁻⁴	21.4	2.3

* The ratio of the relative amounts in urine and feces.

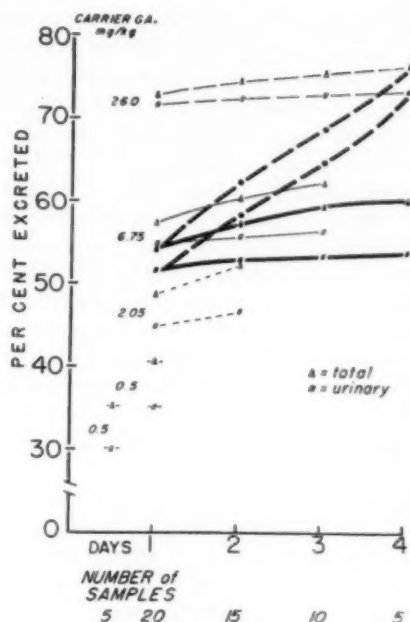


Fig. 14. The urinary and total excretion data of Table X broken down to show the relation of dose of metal to per cent excreted. See text for discussion.

gether with one value from Section X, the last of this series. They demonstrate clearly that an increased dose of gallium was associated with an increased percentage of the dose excreted in the urine during the first twenty-four hours after administration. Despite this increased percentage excretion, the retained milligrams of gallium per gram of tissue increased as the dose increased. Data taken from the clinical studies in Section VI show a similar relationship. There was a definite tendency for a given individual to exhibit a consistently high or low rate of excretion at the different dose levels; age, sex, and severity of illness had no apparent relation to this tendency. The last column of Table XI brings out the fact that relatively more of the dose was excreted by way of the urine as the dose increased. The significance of these two relationships is not evident.

Examination of the excretion data of the preceding experiment revealed a peculiarity

which depends on this dose-excretion relation, namely, that two different average excretion curves could be obtained depending on the choice of method of averaging. The excretion data in Table X are broken down in Figure 14 according to the time of sacrifice and, correspondingly, to the dose of metallic gallium. Only enough Ga^{72} had been given to each group to make possible a count of the tissues. This is a conventional procedure intended to minimize the radiation dose to workers and animals, and to conserve a frequently limited supply of radioisotope. Thus, in Figure 14 the pair of dashed lines at the top represent the total and urinary excretion values of the rats which were given 26 mg./kg., a dose sufficient for sacrifice four days later; the three-, two-, and one-day groups were similarly plotted. The twenty-four-hour excretion values of all rats were averaged without regard to their obvious relation to the size of dose; these points were plotted at the beginning of the heavy solid lines. The gallium excreted by the remaining 15 animals during the twenty-four- to forty-eight-hour period was averaged and added to the respective twenty-four-hour points; the forty-eight- to seventy-two- and seventy-two- to ninety-six-hour excretions by the remaining animals were similarly averaged and added to the preceding values to give the heavy more or less horizontal lines.

Another average excretion curve can be obtained by simply averaging the urinary and total excretion of all 20 rats at twenty-four hours as before, and at forty-eight hours averaging the accumulated excretion values of each of the 15 remaining rats, and similarly at seventy-two and ninety-six hours. This method resulted in the sloping, heavy dashed line in Figure 14. The cumulative excretion data in Tables VII-X were calculated according to the latter method, as is customary in tracer experiments.

Comment: Because of these wide differences in excretion relative to dose, and since the rats with the lowest dose were sacrificed first, both of these "average ex-

cretion" curves are open to question. While one cannot be logically chosen in preference to the other, a choice was made on the basis of the procedure which seemed the more descriptive. If the dose effects were absent, both procedures would give the same result.

There was a strong probability that this effect of dose on excretion extended also to the tissue distribution. Thus, the sequence of differential absorption ratios and the percentage distributions could be an effect of size of dose plus the passage of time, instead of an effect of time alone. Because tissue samples cannot be collected on a daily basis, like the excreta, two special experiments were devised to study this point. One, reported in Section X of this series, made use of carrier-free Ga^{67} to observe what effect the virtual absence of carrier had on the distribution. The other is reported below.

6. *The Distribution of Gallium Citrate: Large Constant Doses of the Radiochemical Preparation ("Same Dose Series")*

Each rat received 28.5 mg. of Ga^{+++} /kg. body weight, of the radiochemical preparation; this provided sufficient Ga^{72} for counting purposes at ninety-six hours and matched the highest dose level in Table X, 26 mg./kg. Six rats were sacrificed twenty-four hours later and 7 each at forty-eight hours and ninety-six hours.

Results: The findings presented in Table XII and Figure 15 agree very closely with the corresponding data in Table X except for the retention-excretion data. This lack of agreement is essentially artificial, in that the average excretion values in Table X were computed from all remaining animals regardless of the size of dose which they received. As pointed out in section 5 above, however, this is a questionable procedure. On the other hand, the pair of dashed lines at the top of Figure 14 opposite the 26 mg./kg. dose level represent an excretion level and pattern nearly identical with that in Table XII.

The differential absorption ratio values for the liver and teeth in this "same dose"

TABLE XII: DISTRIBUTION OF Ga⁷² IN MALE RATS SACRIFICED AT ONE, TWO, AND FOUR DAYS AFTER INTRAVENOUS INJECTION OF GALLIUM CITRATE (pH 7.4), THE "RADIOCHEMICAL" PREPARATION

(Each value is the average of the number of rats at the head of the column. Same dose series)

No. of rats Time sacrificed (hr.)	6 24	7 48	7 96
Dose mg. Ga ⁺⁺⁺ /kg. mc./kg.	28.5 4.8-6.3	28.5 4.4-6.1	28.5 4.4-6.3
Percent of original dose retained	29.5	26.4	24.3
Percent of original dose excreted	70.5	73.6	75.7
Fraction in:			
Urine (%)	94.0	90.7	90.7
Feces (%)	6.0	9.3	9.3
Total organ content in per cent of retained dose			
Blood plasma*	1.2	1.2	0.5
Blood cells	0.2	0.1	0.1
Liver	8.2	6.7	5.5
Spleen	0.1	0.3	0.3
Kidney	2.4	1.4	1.0
Heart	0.3	0.3	0.3
Skeleton†	72.4	77.0	79.5
Remainder	15.2	12.5	12.8

Differential absorption ratios

Blood plasma	0.3	0.3	0.1
Blood cells	Negligible	Negligible	Negligible
Liver	2.4	1.9	1.7
Spleen	0.4	1.4	1.2
Kidney	1.4	1.7	1.1
Femur	10.3	11.3	11.2
Shaft	11.6	13.9	13.1
Ends	8.8	8.7	9.5
Teeth	5.3	7.2	7.1
Lymph nodes	0.2	0.3	0.3
Heart	0.1	0.1	0.1
Lung	0.3	0.4	0.4

* and † See footnotes to Table VII.

series were slightly higher, and for the femur and its components were slightly lower than those in the "variable dose" series (Table X). The differential favoring bone over the next highest tissue was 4 at twenty-four hours and 8 at ninety-six hours; the corresponding ratios in the variable dose series were 4 and 14, respectively. The distribution among the organs in per cent of the retained dose was essentially the same as that for the variable dose series except that the ninety-six-hour value for the skeleton was lower and the liver content was consistently slightly higher.

The curves in Figure 15 are flatter and placed lower on the scale than those in Figure 13. This follows from the higher retention figures of Table X which, as pointed out before, are of uncertain inter-

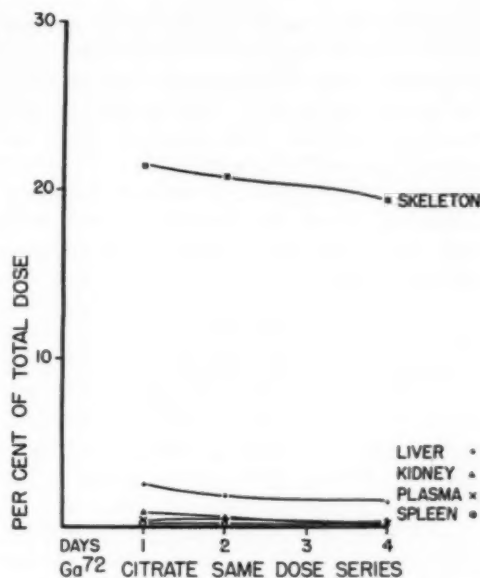


Fig. 15. The same as Fig. 13 except that all animals received 28.5 mg./kg. of carrier gallium.

pretation. When allowance is made for the dose-retention effect, Figures 13 and 15 are quite similar.

Comment: The data demonstrate that the size of the dose of metal had negligible effect on its percentage distribution in the rats and its relative concentration in the various tissues. In terms of weight of metal, however, the gallium retained in the body was greater. For example, 50 per cent retention of a 2.5 mg./kg. dose would be 1.25 mg./kg., in contrast to 20 per cent retention of 25.0 mg./kg., which would be 5 mg./kg.

The clinical implications of this experiment are: A larger dose of inert carrier metal would increase the amount of metal and associated radiation which would pass through the kidneys and urinary tract; this is undesirable. On the other hand, small repeated doses ought to lead to more rapid accumulation of metal in the tissues and limit the radiation dose because of metal toxicity. This is a serious problem where the specific activity of the radioisotope is low, as with Ga⁷².

While this experiment was performed as

a control on the effect of dose of carrier metal, it also partially controlled the possibility that the concomitant dose of radiation influenced the results. The twenty-four-hour data checked with the twenty-four-hour data in Table X from rats receiving only about 2 per cent as much radiation. The experiments in Section X also agree that the radiation dose was not an important factor.

DISCUSSION

According to the experiments reported here, the physicochemical state of the gallium compound influenced the distribution of the metal following intravenous administration. When gallium was given as an insoluble particulate at pH 7.4, the liver and spleen exhibited the highest relative concentrations of the metal. When it was injected as a soluble citrate complex at pH 7.4, the bone showed the highest differential uptake, and this increased during the following three days. The differential favoring bone was the result of the bone taking up initially a larger fraction of the dose and holding it more firmly than the next three highest tissues, the liver, spleen, and kidney. From the standpoint of administering radiation by use of a radioactive isotope, this way of achieving a differential uptake is less preferable than if the bone took up increasing amounts as the experiment proceeded, regardless of the liver and other organs.

The gallium citrate complex prepared by addition of predetermined amounts of reagents gave the highest differential absorption ratios for bone. This was fortunate in view of the difficulties of synthesizing a chemically pure compound with some 500 mc. of an isotope whose half-life is 14.3 hours. The differential absorption ratios obtained with this complex were good enough to justify its use in clinical studies. However, unless a dilute solution of citrate complex is infused very slowly, Ca^{++} as Calcium Gluconate Injection (U.S.P.) should be injected prophylactically.

The data clearly show that a smaller fraction of the dose of gallium was retained

as the dose increased from 0.5 to 28 mg. of $\text{Ga}^{+++}/\text{kg.}$; a similar effect was demonstrated for man. This dose effect, however, apparently was confined to the excretion-retention processes, since neither the differential absorption ratios nor the percentage distribution data were affected.

A secondary result of this primary dose-retention effect is that the excretory and detoxifying mechanisms will be put under stress out of proportion to the increase of absolute amounts of Ga^{72} taken up by the bone. This damage may be automatically limited, however, in that man probably cannot tolerate single doses of gallium, as gallium citrate, in excess of 10 mg./kg. The data here do not indicate what level of carrier gallium might be the best compromise between absolute retention, relative retention, and potential toxicity for man.

Because of the short half-life of Ga^{72} , the differential radiation dose to bone is greatly influenced by the degree of rapidity with which the differential uptake in bone takes place. Obviously, the above data on the rat gave no clues on how rapidly a practical absorption favoring bone will be established in man, if at all. The practical value of these rat data is that they show that such a differential radiation dose can be obtained. Only clinical studies on man, using biopsy or autopsy material, can give the necessary information. Whether osteogenic neoplasms will take up gallium is a still further extension.

SUMMARY

1. Gallium labeled by Ga^{72} was injected intravenously into five different series of rats for the purpose of studying the distribution of the metal in animal tissues. The experiments were designed so as to serve as a prototype for the subsequent clinical studies.

2. Following the injection of GaCl_3 , an acidic (pH 2.0), ionized salt which probably reacted with the blood constituents, there was no distinct differential localization of the element during the first day. Thereafter, the bone had the highest differential

absorption ratio, but this was due to the fact that the other tissues retained their initial content of gallium less firmly than did bone. The excretion was chiefly *via* the kidney and exceeded the 50 per cent level at slightly more than twenty hours after injection. Because Ga⁷² has a 14.3-hour half-life and the development of the differential was slow, the liver and bone received about the same cumulative radiation doses.

3. Gallium alizarinate, a soluble particulate lake or chelate, gave a distribution entirely different from the chloride. The spleen and liver had very high differential absorption ratios; the bone was never more than 20 per cent as high. The ten-day total excretion was 50 per cent, with the urine and feces contributing about equally. This distribution appears to be associated with phagocytosis of the particles by the reticulo-endothelial system, but it is probable that some gallium was loosely bound to the alizarine or some of the lake was broken down by the body metabolic processes. The experiment indicates that a particulate form of gallium or a compound which reacts to give fine particles on injection would not segregate to a sufficiently high degree in bone.

4. A very pure gallium citrate complex prepared on an ion exchange resin had 5 mols of citrate per mol of gallium and required prophylactic use of Ca⁺⁺. More than 50 per cent of the dose was excreted during the first twenty-four hours after injection, chiefly by way of the urine. The bone at twenty-four hours after injection had about the same differential absorption ratio as the liver and spleen, but due to the fact that all other organs retained the metal less firmly than bone, its differential absorption ratio at ninety-six hours was four and seven times greater than that of the next two tissues. The tendency toward a differential favoring bone was definite, but because it developed so slowly, the differential radiation dose to bone was not sufficient for therapeutic purposes.

5. Another type of gallium citrate complex was prepared by adding predetermined

amounts of reagents to the activated Ga⁷². NO₃; it had 1.2 mols of citrate per mol of gallium, but also required a prophylactic injection of Ca⁺⁺. By twenty-four hours after injection the differential absorption ratio of the femur was four times that of the liver and spleen, and at ninety-six hours some fourteen times. As in the previous experiment, this increasing differential was the result of the bone losing relatively less of its initial uptake than did the other tissues. The cumulative differential radiation dose to bone was large enough to warrant trial of this preparation of gallium in man.

6. An examination of the excretion data of the preceding experiments demonstrated that the percentage of the dose which was excreted increased as the size of the dose increased. Also, the ratio of urinary to fecal excretion increased with the size of the dose. The ninety-six-hour urinary excretion by 62 patients showed a similar relation to the dose. These changes in excretion suggested the possibility of an effect of size of dose (metal and/or radiation) on the differential absorption ratios and the distribution of the retained fractions.

The dose-excretion relation was responsible for the observation that different average excretion curves could be obtained depending on the choice of method of calculation.

7. All rats received the same large dose (28.5 mg. Ga⁺⁺⁺/kg.) of the radiochemically prepared citrate complex regardless of the time of sacrifice. The excretion pattern corresponded to that of animals in the preceding series which received similar high doses. On the other hand, the differential absorption ratios and the percentage distribution of the retained doses were similar to those of animals which had received doses only 2 to 5 per cent as large. Thus, large doses of carrier gallium had no significant effect on the distribution of the metal in the tissues, although the excretory pattern was definitely affected. Concomitant variations in the radiation dose appeared to be unimportant in causing these dose effects.

8. The rat data indicate that the radio-

chemical preparation of gallium citrate is suitable for use in clinical studies. They do not provide information as to what dose

will give the highest specific uptake in bone consonant with the least metal toxicity and total-body irradiation.

VI. Clinical Studies with Gallium⁷²

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BACKGROUND OF THE CLINICAL TRIAL OF GALLIUM

Since radiogallium seemed to have selective deposition in bone and primarily in centers of osteogenic activity, it was considered worth while to investigate the therapeutic possibilities in human tumors involving the skeletal system. Since there was very little previous clinical experience with this isotope, a flexible program was started and was continuously modified as experience indicated.

In general, two groups of patients were studied. In one group a definite attempt was made to produce a therapeutic effect with Ga⁷² treatment. The second group was composed of patients in whom no therapeutic attempt was made, but rather in whom localization or uptake of Ga⁷² in the various tumors or sites was studied. All the patients in both groups, with one exception, had ultimately fatal neoplasms not amenable to curative surgery or radiotherapy. Those in the "therapeutic" group were, in general, in a more advanced stage of disease and were completely beyond even palliation from conventional forms of therapy. In many instances, the initial tracer studies helped to determine whether or not a prolonged therapeutic attempt would be undertaken. Bone tumors of all types which were available to us, both primary and metastatic, were studied, and occasionally tumors of other types when opportunity arose. In this latter group were three cases of chronic leukemia, one of Hodgkin's disease, and a few other neoplasms without skeletal involvement.

MODE OF ADMINISTRATION AND DOSAGE

The radioactive gallium was available only on Mondays and Thursdays, because of the schedule of the Oak Ridge National Laboratory Reactor Division. Because of the 14.3-hour half-life, the isotope was administered shortly after it was removed from the reactor. The program of bi-weekly treatment was believed to be fairly satisfactory and might have been chosen even if the availability of the isotope had not been a determining factor. It would be quite impractical to give a therapeutic amount in a single dose. Such a dose would produce personnel hazards insurmountable at the present time and, because of individual sensitivity to radiation effect, it would be impossible to estimate accurately the proper dose. Further, the toxicity of the stable gallium precluded giving all of the desired dose at a single time. Fractional treatments at three- and four-day intervals appeared to allow for a reasonable protraction of the treatment and adjustment of the individual dose; but it is pointed out that this was a rather arbitrary factor in the experimental trials.

The gallium was always administered intravenously. Very little work has been done on the absorption of gallium from the gastrointestinal tract, and it might be feasible to give this material orally. However, the extremely short half-life makes this route of administration undesirable. Even if the gallium were very rapidly absorbed, the stomach and upper small intestine would receive a high dosage of radiation. It is obvious that the ratio of absorption time to half-life is an important factor in determining the relative amount of radiation delivered to the stomach and small intestine as compared with other tis-

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sues of the body; when this ratio is high, as it must be in the case of a very short half-life isotope, there is a distinct disadvantage in the oral route. The intravenous route also has the advantage of assuring a known dosage.

Normal tissue and whole-body tolerances for amounts of radiogallium necessary to produce a significant effect upon malignant tissues were unknown. Preliminary calculation and small-animal experiments had indicated that the accepted radiation dosimetry as applied to other isotopes would be of little value in calculating radiation dosage to tissues. It was therefore necessary to utilize the hematologic picture to assess the damaging effects of whole-body irradiation, and clinical and roentgenographic experience in evaluating a therapeutic response. In the "therapeutic" group, doses which were believed to be moderate were given and gradually increased to a toxic level. In two patients our estimates of safe dosage limits were in error and the radiogallium is believed to have hastened death.

The doses, which ranged from 10 to 100 mc., were always given by an intravenous drip apparatus described earlier in this study. The material was poured into this apparatus from a bottle held with tongs, and no close handling of the radioactive gallium was necessary. Doses below 10 mc. were generally given with a 10 c.c. syringe contained in the metal syringe protector which has previously been described. The large doses could be measured quite satisfactorily by means of a Lauritsen electroscope. The small doses represented fractional volumes of larger samples assayed by the electroscope, and these small doses often were not very satisfactorily measured in the syringe, because of bubbles, which obscured the exact degree of filling and also because of the residual gallium which remained in the syringe after injection.

PROGRAM OF STUDY

In all patients studied the diagnoses were confirmed by histologic sections, ex-

cept for a few with malignant plasmacytoma and leukemia, in whom the diagnosis was based upon cytologic studies. The studies in the Medical Division included a routine history and physical examination. Routine urinalyses and extensive x-ray examinations were performed. Blood chemistry examinations included determinations of serum calcium, phosphorus, alkaline and acid phosphatase. Kidney and liver function tests were obtained in the patients who were to receive large amounts of gallium. Additional work was done as seemed desirable in individual cases.

Frequent—in some cases daily—hematologic studies were performed. These included a white count, differential count, chamber eosinophil count, and estimate of platelets. At less frequent intervals, hemoglobin determinations, hematocrit readings, and red cell counts were done. The bone marrow from many of the patients was examined before, during, and after therapy. The blood chemistry determinations, particularly calcium, phosphorus, and phosphatase, and the studies of liver and kidney function were repeated during and after the courses of the therapy in an effort to detect various changes due to radiation or stable metal toxicity. Repeated x-ray examinations were probably the most important method of evaluating the course of the disease. Thirty-five-millimeter colored photographs were also used in some patients to show comparative sizes of external lesions.

METHODS OF STUDY OF LOCALIZATION OF GALLIUM⁷²

Methods used to determine the localization of gallium⁷² varied with the individual patient, depending upon the type of lesion and suitability for biopsy. In many patients external radioassays were made. Most of these were done with a highly collimated Geiger-Müller tube, which made possible rather exact localization. Patients who received very small doses of gallium could not be studied with this instrument because of its relative insensitivity, and

for these a tube with less directional shielding was used.

Biopsies were performed upon many patients, usually forty-eight hours after the last dose of gallium. This time interval was rather arbitrarily chosen; it was believed to be long enough to allow differential localization and short enough to give suitable levels of activity for study with a reasonable dose to the patient. In most instances an attempt was made to obtain a portion of the neoplastic lesion with an area of adjoining normal tissue, which for the most part was bone. We also tried to obtain skin, muscle, and any other easily available, relatively normal tissue to serve as a basis of comparison. Blood appeared to be a most suitable normal tissue for this purpose, and blood radioactivity levels were obtained simultaneously with the biopsies in many cases. In each biopsy study, the tissues were carefully studied grossly and divided into portions for specific determinations. Radioassays were made upon acid digests of tissue, and for each type of tissue an adjacent area was saved and labeled for histologic sections. Gross and microscopic autograms were also prepared on many of the biopsy specimens, and some of the tissues from which gross autograms were made were subsequently studied by histologic sections corresponding to the various areas of the gross autogram. Routine histologic sections were made on every biopsy, but during the early part of the study these were not always chosen and labeled in such a way that the exact tissue at the points of activity in the gross autogram could be identified.

Autopsy material was obtainable for 11 of the patients who received large doses. When feasible, an effort was made to administer a dose of radioactive gallium at a suitable time before the expected time of death so that radioassays could be made. In one patient radioactive phosphorus and gallium were given simultaneously, in another sulfur and gallium, in an effort to study comparative distributions. At the autopsies, the usual gross and histologic studies were carried out, and extensive

radioassays and autoradiograms were also obtained.

TOXIC MANIFESTATION

One of the chief problems throughout this study was the evaluation of the toxic manifestations which developed. Since there was no previous human experience with stable gallium, the manifestations of toxicity to the metal were unknown. The characteristics of total-body irradiation damage or radiation damage arising primarily from an isotope localized in bone were quite well known; but since there is no way of measuring the effective dosage to the bone marrow of this type of radiation, there is a lack of quantitative data to evaluate chemical *versus* radiation effects. Because of the fact that it was not possible to obtain a high specific activity of Ga^{72} , it was necessary to give amounts of stable gallium which we believed to be somewhat toxic.

Patients usually tolerated the first one or two doses very well and many of them said they could not notice any effects whatever from the treatment. Some felt rather drowsy during the six or eight hours following the intravenous infusion. This drowsiness tended to persist uniformly in individuals who received many injections. Patients who received only three or four injections of gallium did not notice delayed effects. Those who received "therapeutic" amounts began to notice anorexia after the third or fourth dose, and with continued treatments severe nausea and vomiting developed. Some patients maintained good appetites but vomited promptly after each meal. Others refused to eat any significant amount after they were well into the course of treatment. Many could eat breakfast but would not take any other meal during the day. As the course of treatment progressed, vomiting immediately after administration of the dose became prominent. In some individuals whose personalities did not lead us to believe that they would be particularly open to suggestion, a "conditioned reflex" vomiting occurred as soon as they saw the gal-

lium coming into the room. A frequent symptom was a peculiar metallic taste during the period of treatment. The gastrointestinal symptoms were the most uniform manifestations of toxicity with large doses. Two young patients, however, who received rather large amounts had only minimal anorexia.

Prominent dermatologic changes were seen in many patients, but they were not uniform in type or predictable in degree. They usually developed after the fifth or sixth injection of gallium or within the second, third, or fourth week of treatment. Mild degrees of folliculitis were sometimes seen, while in other instances an extensive maculopapular rash developed, and in a few cases there was a generalized exfoliative dermatitis. Itching was very severe with almost all of these lesions. Some of them were associated with rather prominent edema of the skin and subcutaneous tissue. All of the dermatologic manifestations cleared up within a few days after cessation of therapy.

In two patients very small retinal hemorrhages were noted during the latter part of the gallium therapy.

Hematologic changes were prominent and were usually of primary importance in determining when the treatments should be discontinued. After from one to five "therapeutic" doses of gallium, depending on the dose size, the changes in the blood picture became apparent. The first of these changes was a relative lymphopenia, often associated with a prompt decrease in the total white cell count. Somewhat later the platelets decreased in number. Slight changes in the red cell values began to occur quite promptly, but the more severe effects were delayed and the anemia usually reached its greatest severity some weeks after the end of the course of treatment. Bone marrow studies done before treatment and during the greatest hematologic depression showed that the gallium treatment caused a profound hypoplasia of all the marrow elements. Red cell precursors, plasma cells, reticulo-endothelial elements, and a few other primitive cell types were

the chief nucleated forms persisting in these very hypoplastic marrows.

Recovery was seen in the hematologic picture rather soon after cessation of gallium therapy in most instances. The red cell regeneration, however, lagged behind that of the white cells and platelets. Clinical manifestations of the severe bone marrow depression consisted of a susceptibility to infection, particularly pneumonia, and in some instances a prominent bleeding tendency. Of two patients who died during profound bone marrow depression, one had evidences of both bleeding and infection, while in the other infection was most prominent. These two patients died in spite of antibiotics, blood transfusions, and toluidine-blue therapy.

In the other patients, who had milder bone marrow depression but prominent gastrointestinal symptoms, many types of symptomatic therapy were used, including pyridoxine, Dramamine, sedatives, antihistaminics, and intravenous fluids. Several patients with bone marrow depression received blood transfusions during the course of therapy.

It was difficult to determine to what extent the toxic manifestation could be attributed to radiation alone and to what extent they were caused by stable metal toxicity. There was little doubt that both factors were important, but the relative role played by each was difficult to quantify. A single patient, No. 110088, was given a series of injections of stable gallium comparable to those in a therapeutic course of radioactive gallium. A small tracer amount of radiogallium was administered with each dose, for measurement purposes. It was believed that this patient received too little radiation to be significant clinically. In general, he tolerated the course of treatment with much less evidence of toxicity than did the patients who received a large amount of radiation. He maintained his weight, although he had some nausea and anorexia. During the course of treatment, he had a viral or fusospirochetal infection, which was believed to be incidental, but which impaired his general

TABLE XIII: SUMMARIES OF CASES IN WHICH Ga⁷² WAS GIVEN IN LARGE DOSES
(N.D., No data; 0, None; +, Little; ++, Moderate; +++, Pronounced)

Case, Sex, and Age	Diagnosis	Mc. Ga ⁷² Mg./Kg.	Hema- tologic Depres- sion	Anorexia Nausea Vomiting	Skin Rash	Evidence of Concentration in Tumor			Clinical Impression
						Ex- ternal Count- ing	Opera- tion	Autopsy	
P.D.G. 010003 ♀ 14	Osteogenic sarcoma, with pulmonary metastases.	50.3 mc. 251.4 mg.	0	0 (due to gallium)	0	++	N.D.	+++	Patient received a relatively small amount of gallium when in nearly terminal condition. No evidence of effect on course of the disease
C.R.M. 010007 ♂ 40	Primary amputated Plasma-cell myeloma	8.5 mg./kg. 162.5 mc. 813.0 mg. 13.7 mg./kg.	+	+	+++	0	N.D.	N.D.	
W.C.A. 010008 ♂ 43	Osteochondrosarcoma. Primary present	511.6 mc. 2511.0 mg. 33.0 mg./kg.	++	+++	++	+	++	N.D.	Tumor became softer and larger during course of therapy. No definite effect of gallium on course of disease
T.F.P. 010009 ♂ 26	Osteogenic sarcoma	383.4 mc. 1889.7 mg. 28.6 mg./kg.	++	++	+	++	+	N.D.	Death at home. No autopsy No discernible effect of gallium on clinical course Death elsewhere seven and a half months after first tracer Ga ⁷² . Autopsy performed elsewhere
H.D. 010012 ♂ 19	Osteogenic sarcoma. (?) Pulmonary metastases	606.6 mc. 2390.5 mg. 30.1 mg./kg.	+++	+++	+	0	0	N.D.	Pneumonectomy about two weeks after last dose of gallium. Lung showed lesions, previously pre- sumed to be metastases, to be necrotic nodules surrounded by fibrous capsule containing a few questionable neoplastic cells
A.S. 010013 ♂ 64	Plasma-cell myeloma	166.0 mc. 662.1 mg. 12.9 mg./kg.	++	+	+	N.D.	N.D.	+	Patient well twelve months postoperatively Death during course of therapy from acute ne- phrosis, mild subarachnoid hemorrhage, and cerebral edema complicating plasma-cell mye- loma. Gallium of no benefit. Not considered cause of death
D.H. 010016 ♀ 12	Osteogenic sarcoma. Primary present	730.8 mc. 3125.1 mg. 89.2 mg./kg.	+++	+	0 to +	+++	+++	+++	Death four months after first tracer dose Ga ⁷² . Autopsy
L.K. 010019 ♂ 54	Osteogenic sarcoma	554.8 mc. 2400.4 mg. 31.0 mg./kg.	+++	+++	+++	+++	+	N.D.	No evidence that gallium influenced course of disease Death eight months after first tracer dose of Ga ⁷² . Autopsy
D.A. 010023 ♂ 17	Osteogenic sarcoma. Primary amputated. Pul- monary metastases	290.4 mc. 1595.5 mg. 30.4 mg./kg.	++	++	0	0	0	+	Slight tenderness of tumor at end of treatment. No demonstrable effect of therapy No effect of gallium on clinical course noted Death five weeks after first tracer dose Ga ⁷² . Autopsy

(Table continued on pages 576 and 577)

health temporarily. His blood picture failed to show the profound depression observed in patients given high doses of radiation with a similar total gallium dosage, but he did show a rather prominent anemia and a mild depression of the white count. A very definite skin rash developed.

In summary, it appears that the toxic reactions seen in the series of patients given large doses of gallium can be interpreted approximately as follows:

The profound bone marrow depression is characteristic of radiation damage and is probably chiefly caused by radiation, though an element of stable metal toxicity may also be contributory. The skin rash, on the other hand, seems undoubtedly a manifestation of toxicity of stable gallium. The gastrointestinal symptoms probably are due both to radiation damage and stable gallium toxicity.

LABORATORY DATA DURING AND AFTER THERAPY

Routine urinalysis, performed repeatedly in all cases, showed no distinct changes related to the Ga⁷². Occasional one- to three-plus albuminuria was seen transiently during or immediately following treatment. In only 2 cases did this appear to be distinctly related to the Ga⁷² administration. Blood non-protein nitrogen determinations showed no change during and following therapy. A considerable number of patients had elevated blood alkaline phosphatase levels before treatment. Of 10 in this group for whom multiple determinations were available, none showed a consistent change which could be related to gallium treatment. Three patients with carcinoma of the prostate had repeated blood tests for acid phosphatase and, while there was considerable fluctuation in levels for each patient, there was no apparent relation to the course of gallium therapy. Liver function, in so far as it was reflected by thymol turbidity and cephalin cholesterol flocculation tests, showed no alteration.

The fact that many of the patients in this series had serious and increasing meta-

bolic alterations due to progressive neoplastic growth made evaluation of gallium damage difficult. It appeared clear that during and immediately after treatment changes in kidney and liver function, if present, were slight in comparison with bone marrow injury.

EXTERNAL RADIATION MEASUREMENTS

In many instances, radiation measurements were made over various areas of the patients' bodies, usually twenty-four or forty-eight hours after Ga⁷² administration. The information gained from these studies correlated well with radioassays and autoradiographs made upon tissues obtained at biopsy or autopsy, but the external counting determinations were relatively insensitive and failed to indicate slight localized differences in concentration or to show the true magnitude of pronounced variations. Even over lesions which showed a local concentration of manyfold by biopsy or autopsy assays, it was unusual to obtain external counting levels more than three times those of the comparable uninvolved area.

GROUP OF PATIENTS SUBJECTED TO TRIAL OF THERAPY WITH LARGE DOSES OF GALLIUM⁷²

Table XIII presents a brief summary of material on 21 patients who were given significant doses of radioactive gallium. The information is largely self-explanatory. The first column gives the patient's initials, his hospital number, sex, and age. The second column is the diagnosis based upon histologic or cytologic material. The third column includes the dosage of gallium in millicuries, total milligrams of gallium given, and the milligrams per kilogram of body weight. The next column indicates the severity of hematologic depression attributed to the gallium injected. The symbols +, ++, and +++ were used to indicate in a general way the severity of the hematologic depression. The patients recorded as showing a 3-plus blood change all had white cell counts below 1,000 per cubic millimeter for a significant period of time. The next column indicates the

TABLE XIII: (Continued)

Case, Sex, and Age	Diagnosis	Mc. Ga ⁷⁵ Mg, Ga, and Nig./kg.	Hema- tologic Depres- sion	Anorexia Nausea Vomiting	Skin Rash	Evidence of Concentration in Tumor			Clinical Impression
						Ex- ternal Count- ing	Opera- tion	Autopsy or Biopsy	
D.A.S. 010044 ♂72	Carcinoma of prostate, with bone metastases. Previous prostatectomy	462.9 mc. 1837.9 mg. 31.5 mg./kg.	++ to +++	++	++	++	+++	N.D.	Patient was on maintenance dose of stilbestrol, not changed for gallium therapy. Some subjective improvement following course of gallium, with decrease in bone pain
E.G. 110047 ♀57	Carcinoma of breast, with bone metastases. Previous mastectomy	517.1 mc. 2392.9 mg. 43.9 mg./kg.	+++	+	++	N.D.	++	N.D.	Patient was on testosterone throughout. Also received localized x-ray therapy during gallium course. Slight transient decrease in pain at end of course of gallium Death at home five months after first tracer dose Ga ⁷⁵ . No autopsy
J.F. 110049 ♂51	Adenocarcinoma of right kidney, with metastases to bone	490.7 mc. 2453.4 mg. 53.9 mg./kg.	+++	+++	++	N.D.	+	0	Patient died during severe hematologic depression. Gallium may have hastened death. No evidence of any benefit Death two months after first tracer dose of Ga ⁷⁵ . Autopsy
L.W. 110053 ♀17	Osteogenic sarcoma. Primary amputated. Pulmonary metastases	442.2 mc. 4601.8 mg. 66.7 mg./kg.	++ to +++	0	0	0	N.D.	N.D.	Pulmonary metastases enlarged during and following treatment. No evidence of any effect of treatment on course of the disease
J.D.P. 110054 ♂66	Carcinoma of prostate, with bone metastases. Previous prostatectomy and orchiectomy	443.6 mc. 2217.8 mg. 54.1 mg./kg.	+++	+++	0	+++	+++	No suitable bone samples at autopsy	Transient subjective benefit at end of course of gallium. Then rapid deterioration and death Death two months after first tracer dose Ga ⁷⁵ . Autopsy
J.M. 110055 ♂26	Chronic myelocytic leukemia. Late stage	571.8 mc. 2868.6 mg. 42.6 mg./kg.	++	0	0	N.D.	N.D.	(Autopsy assays for Au ¹⁹⁸)	Patient had unusual leukemic lesions, chiefly destructive, involving many bones. The gallium treatment caused some apparent decrease in bone pain temporarily Death two months after first tracer dose of Ga ⁷⁵ . Autopsy
E.E.R. 110057 ♂62	Carcinoma of prostate. Bone metastases	454.2 mc. 2266.9 mg. 31.2 mg./kg.	+++	+	+	+++	+++	(Autopsy, no assays)	This patient said that his pain greatly diminished during his treatment. There was no objective evidence of improvement. Severe bone marrow depression developed from the gallium and this was believed to contribute to his death Death two months after first tracer dose of Ga ⁷⁵ . Autopsy
B.D. 110061 ♂17	Osteogenic sarcoma. Lung metastases. Primary present	777.4 mc. 3792.1 mg. 70.9 mg./kg.	++	+	0	+	+++	0	Primary lesion (rt. leg) amputated after dose of gallium. Metastatic pulmonary lesions continued to grow during gallium therapy Death four months after first tracer dose Ga ⁷⁵ . Autopsy

P.H.R. 110067 9 54	Carcinoma of bladder, Bone and lung metas- tases	312.2 mc. 1665.2 mg. 23.6 mg./kg.	++ to +++	+	0	N.D.	++	++	N.D.	Patient stated that he had temporary but definite relief of bone pain during gallium therapy. X-ray evidence of some recalcification of bone lesion in pelvis, but pulmonary metastases continued to grow during treatment. New bone lesions developed a few weeks after cessation of treatment. Death elsewhere six months after first tracer dose of Ga ⁷² . No autopsy data.
F.T. 110073 9 13	Osteogenic sarcoma. Lung metastases. Primary present	272.7 mc. 1367.5 mg. 33.4 mg./kg.	++	+	0	++	++	++	0	Primary lesion amputated after test dose of gallium. Subsequent course of gallium treatment, during which the metastases grew rapidly. Death two and a half months after first tracer dose of Ga ⁷² . Autopsy.
B.H. 110079 9 57	Carcinoma of breast. Bone metastases. Pre- vious mastectomy	210.7 mc. 923.7 mg. 14.9 mg./kg.	++	+++	0	N.D.	0 to +	0	0	Patient tolerated only small amount of gallium. Rapid down-hill course apparently not influenced by gallium. (X-ray therapy given for local pain.) Estinyl throughout. Death one and a half months after first tracer dose of Ga ⁷² . Autopsy.
P.J. 110087 9 52	Carcinoma of breast. Bone metastases. Pre- vious mastectomy	287.3 mc. 1278.3 mg. 19.5 mg./kg.	+++	++	0	0	+	+	N.D.	No change in bone lesions during or following gallium. No relief of bone pain.

severity of anorexia, nausea, and vomiting, as they were attributed to the gallium treatment. The column indicating skin lesions needs no explanation. The next three columns indicate the degree of localized gallium uptake in the tumor. The concentration of gallium in each tumor is compared with that of available normal tissue.

PATIENTS STUDIED WITH TRACER DOSES

Another, entirely separate group of patients, 34 in number, were studied with tracer doses only of Ga⁷² (Table XIV). Some of these patients were being considered for a trial of therapy with this isotope. The remainder were patients admitted to the hospital for other forms of study or treatment, to whom it was possible to give the Ga⁷² tracer dose as an additional study.

THREE CASE REPORTS

Only the first of the following 3 case reports is presented as a typical example. It is of a patient with osteogenic sarcoma who showed concentration of gallium in the lesions but who failed to have apparent benefit from the treatment. The second is of an unusual case unlike any other in the series. The third case is that of the only patient given large doses of stable gallium.

CASE I: History: H. D. (No. 010016) was a 12-year-old colored school girl whose case is summarized in Figure 16. She was admitted on Aug. 23, 1950, with a history of pain and swelling of the left thigh beginning about one year prior to admission. In July 1950, upon the basis of x-ray studies, a diagnosis of osteogenic sarcoma of the femur with pulmonary metastases was made. The patient had received no radiation therapy or surgical treatment prior to admission.

Physical Examination: Temperature 37° C., pulse 70, respirations 22, blood pressure 104/78. The patient was slightly underweight but appeared to be in fairly good general condition. Her lungs were normal on physical examination. There was a large fusiform mass on the left thigh involving the distal half of the femur. The circumference of the thigh at the level of this mass was 37 cm., as compared with 27 cm. at the corresponding level on the normal side.

X-Ray Studies: Films showed a characteristic picture of osteogenic sarcoma of the femur. There were numerous pulmonary nodules

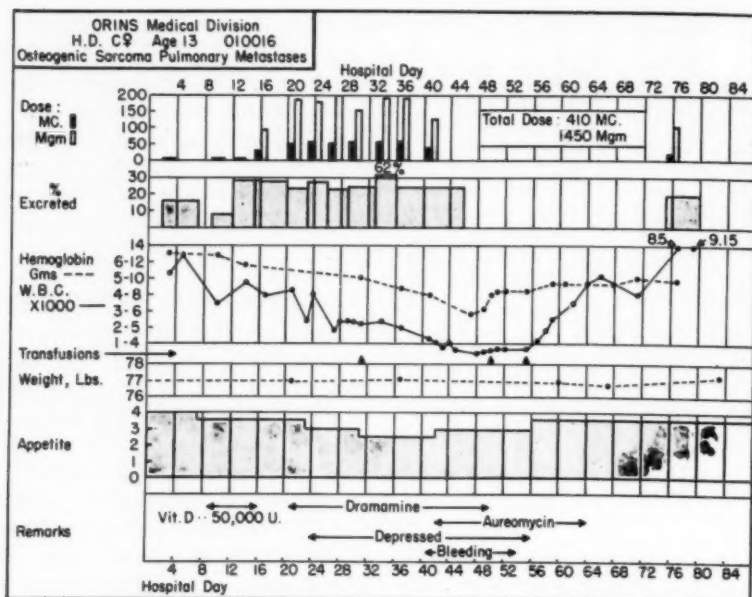


Fig. 16. Summary of Case No. 010016.

Course: Intravenous gallium citrate was given with 5-10 ml. of 10 per cent calcium gluconate intravenously before each dose.

Date	Dose (mc.)	Mg. of Gallium
8-18-50	1	9
8-25-50	1	9
8-28-50	1	5
8-31-50	29	90
9- 5-50	52	184
9- 7-50	54	179
9-11-50	49	204
9-14-50	54	155
9-18-50	56	195
9-21-50	53	199
9-25-50	41	123
9-30-50	22	102
TOTALS	413	1454

External counting studies showed counts over the lesion in the femur to be about three to four times the level on the normal side and two to three times the level over the trunk. No definite localization of the chest lesions could be shown by external counting. During this treatment, the patient suffered no severe nausea or vomiting, though she did complain of anorexia and malaise. During the period of greatest depression in the bone marrow, late in August and early in September, she had a distinct bleeding tendency, with some oozing from the gums and nose.

She was given Aureomycin and blood transfusions during this period.

The laboratory findings during treatment were as shown on the following page.

During the gallium treatment the urine showed varying amounts of albumin up to 3+. On discharge it was negative.

After completion of the course of gallium, the patient rapidly improved and seemed to feel somewhat better than she had before the beginning of the treatment. She was discharged on Nov. 10, at which time the hemoglobin was 9.5 gm., white cell count 9,150. She was quite well and free from pain for several weeks. Early in 1951, she had increasing pain in the left femur and her general condition became poorer. She returned on Feb. 14, 1951.

Another extensive course of gallium⁷² was given, bringing the total dose to 730 mc. Pronounced hematologic depression again occurred. Amputation of the leg with the primary lesion was done after the first dose of gallium and autograms and assays were obtained. Histologic sections were characteristic of a highly cellular osteogenic sarcoma. The patient died of extensive pulmonary metastases while she was showing toxic effects from her second course of gallium. She received a small dose of the isotope shortly before death for tissue radioactivity assays and autograms.

At autopsy there were found multiple pulmonary metastatic nodules, which practically replaced normal lung; these nodules showed a considerable amount of calcification.

	Aug. 17, 1950	Sept. 25, 1950 (During gallium treatment)	Feb. 15, 1951 (Two and a half months after 1st course of Ga ⁷²)
R.B.C.	4.17 million	3.00 million	3.48 million
Hemoglobin	13.3 gm.	8.0 gm.	8.5 gm.
Hematocrit	41%	24%	28%
W.B.C.	5,200	1,350	9,250
Differential count			
Band neut.	2.0%	5.0%	4.5%
Segmented	44.0	41.0	76.0
Lymphocytes	45.0	45.0	8.0
Monocytes	7.5	7.0	10.0
Eosinophils	1.0	0	1.5
Basophils	0.5	(greatly decreased)	(slightly increased)
Thrombocytes	(slightly increased)		
Red cells	N	N	
		Some "irritation" lym- phocytes. Neutro- phils with large granules or nuclear fragments	Moderate anisocyto- sis, poikilocytosis, and hypochromia. Some young mono- cytes

After Sept. 25, the white cell count fell still lower than on that date, reaching 500 per cu. mm. After about a week at very low levels, it gradually rose.	Aug. 29-31, 1950 (Before treatment)	Oct. 19, 1950 (After treatment)
Alkaline phosphatase	6.3 Bodansky units	7.7 Bodansky units
Acid phosphatase	4.6 K.-A. units	2.3 K.-A. units
Cephalin cholesterol flocculation		
24 hours	+++	0
48 hours	++++	+++
Thymol turbidity	12.5 units	10.4 units

Comment: This is a case of osteogenic sarcoma with extensive pulmonary metastases in a young individual who received two extensive courses of Ga⁷². The primary lesion and metastases continued to grow rapidly during and after treatment.

CASE II: History: D. H. (No. 010012) was a 19-year-old colored male whose case is summarized in Figure 17. He was admitted Aug. 3, 1950. He had a history of injury to his left femur about one year before admission, followed by pain and swelling, and an x-ray diagnosis of tumor involving the left femur was made in July 1949. Histologic studies showed on osteogenic sarcoma. A high thigh amputation was done in October 1949. In June 1950, there was x-ray evidence of a nodule in the left lung. This had enlarged on subsequent x-ray examination.

Physical Examination: Temperature 37° C., respirations 18, blood pressure 120/80. The patient was a well nourished, young Negro male, who was

able to get around quite well with crutches. The left leg had been removed at the hip and the amputation wound was well healed. Physical examination revealed no further noteworthy abnormalities.

X-Ray Studies: 8-8-50: A postero-anterior chest film revealed a small rounded density in the left lower lung field, measuring approximately 1.5 cm. in greatest diameter, but with no evidence of calcification. A very small pneumothorax and pleural effusion were also seen in the left side.

8-24-50: Re-examination of the chest showed the previously described nodule in the left lower lung field to be approximately the same size as on the previous examination. The pneumothorax had increased and there was slightly more fluid present than on the previous examination. The heart size and shape had changed considerably, probably as the result of the pneumothorax.

10-3-50: Re-examination revealed some increase in the size of the nodule, which now measured approximately 3 cm. in greatest diameter. There were still some pneumothorax and a small amount of pleural fluid in the left costophrenic angle.

TABLE XIV: SUMMARIES OF CASES IN WHICH Ga^{72} WAS GIVEN IN TRACER DOSES
(N.D., No data; 0, None; +, Little; ++, Moderate; +++, Pronounced)

Case, Sex, and Age	Diagnosis	Ga ⁷² in mc.	Per cent Excreted	Evidence of Concentration in Tumor			Additional Data and Remarks																																					
				External Measurement	Autopsy	Biopsy																																						
E.H.N. 010018 ♀46	Plasma-cell myeloma	(a) 1.0 (b) 23.5 (c) 23.5	49.2 24.9 14.7	N.D.	Autopsy but no gallium assay	N.D.	Sulfur studies done (S ³⁵ in yeast) after Ga ⁷² test doses. Autopsy with S ³⁵ assays																																					
T.C.R. 010020 ♀42	Lymphosarcoma	(a) 1.0	9.2	N.D.	Autopsy but no gallium assay	N.D.	Treated with P ³² after trial gallium dose. Autopsy P ³² studies																																					
O.B. 010021 ♂43	Chronic lymphocytic leukemia	(a) 1.9 (b) 20.0	24.4 33.3	0	N.D.	N.D.	Patient treated with P ³² and corti- sone. No further gallium study																																					
V.P.W. 010024 ♀52	Lymphosarcoma	(a) 1.5	4.6	N.D.	Autopsy but no gallium assay	N.D.	Single tracer dose for excretion studies. Later x-ray therapy. Autopsy. No isotope distribu- tion study																																					
A.G.W. 010025 ♀70	Undifferentiated carci- noma of thyroid	(a) 1.0	10.5		Autopsy but no gallium assay	N.D.	Studied chiefly with I ¹³¹ . Given 1 mc. gallium for excretion. Tis- sue assayed for I ¹³¹																																					
J.R.U. 010026 ♂56	Chondrosarcoma	(a) 2.2 (b) 27.9 (c) 22.0	7.4 20.6 21.0	0	N.D.		Biopsy twenty-four hours after 27.9 mc. Ga ⁷² <table><tr><td>Tissues</td><td>cts./Gm.</td><td>μc./Gm.</td></tr><tr><td>Fat</td><td>708</td><td>0.009</td></tr><tr><td>Skin</td><td>1,736</td><td>0.022</td></tr><tr><td>Tumor</td><td>855</td><td>0.011</td></tr><tr><td>Muscle</td><td>731</td><td>0.009</td></tr><tr><td>Cartilage</td><td>5,536</td><td>0.071</td></tr></table>	Tissues	cts./Gm.	μc./Gm.	Fat	708	0.009	Skin	1,736	0.022	Tumor	855	0.011	Muscle	731	0.009	Cartilage	5,536	0.071																			
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Muscle	731	0.009																																										
Cartilage	5,536	0.071																																										
L.C. 010027 ♀35	Carcinoma of breast. Lung metastases with pleural effusion	(a) 1.9 (b) 22.3	6.0 16.4	0	N.D.	N.D.	Studied chiefly with Au ¹⁹⁸ . Given 1.4 mc. gallium for excretion and 22 mc. prior to external counting																																					
M.T.V. 010028 ♀66	Plasma-cell myeloma	(a) 1.0 (b) 46.9	12.7 24.3	0	N.D.	N.D.	Treated with urethane after gal- lium study																																					
J.M.S. 010029 ♀3	Neuroblastoma of ad- renal	(a) 10.2	23.2	0	Autopsy but no gallium assay	N.D.	Studied chiefly with P ³² . Autopsy distribution studies for P ³² . Autopsy here. Tissue assay for P ³²																																					
M.T.M. 010030 ♂62	Carcinoma of prostate. Bone metastases	(a) 1.3 (b) 48.7	3.6 11.2	+	N.D.	++	Biopsy, trephine twenty-four hours after 48.7 mc. gallium <table><tr><td>Tissue</td><td>cts./Gm.</td><td>μc./Gm.</td></tr><tr><td>Bone metastases</td><td>29,000</td><td>0.373</td></tr><tr><td>Normal bone</td><td>7,720</td><td>0.099</td></tr></table>	Tissue	cts./Gm.	μc./Gm.	Bone metastases	29,000	0.373	Normal bone	7,720	0.099																												
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Normal bone	7,720	0.099																																										
N.J.S. 010031 ♀53	Carcinoma of ovary	(a) 1.3 (b) 23.7 (c) 20.6 (d) 18.0	2.3 0.42 6.8 17.6	N.D.	Autopsy but no gallium assay	+	1. Biopsy twenty-four hours after 23.7 mc. Ga ⁷² <table><tr><td>Tissue</td><td>cts./Gm.</td><td>μc./Gm.</td></tr><tr><td>Cervical tumor</td><td>13,400</td><td>0.172</td></tr><tr><td>Normal cervix</td><td>1,025</td><td>0.013</td></tr><tr><td>Sigmoid tumor</td><td>9,073</td><td>0.117</td></tr><tr><td>Normal sigmoid</td><td>3,185</td><td>0.041</td></tr></table> 2. Biopsy twenty-four hours after 18 mc. Ga ⁷² <table><tr><td>Tissue</td><td>μc./Gm.</td></tr><tr><td>Liver</td><td>0.17</td></tr><tr><td>Fascia, above umbilicus</td><td>0.04</td></tr><tr><td>Tumor, necrotic</td><td>0.14</td></tr><tr><td>Muscle, rectus</td><td>0.02</td></tr><tr><td>Tumor retroperitoneal node</td><td>0.11</td></tr><tr><td>Tumor retroperitoneal node</td><td>0.13</td></tr><tr><td>Fat, from colon</td><td>0.10</td></tr><tr><td>Abdominal fluid</td><td>0.04</td></tr><tr><td>Subcutaneous tissue</td><td>0.02</td></tr><tr><td>Skin</td><td>0.05</td></tr></table> Death three and a half months fol- lowing first biopsy. Autopsy. Au ¹⁹⁸ distribution study	Tissue	cts./Gm.	μc./Gm.	Cervical tumor	13,400	0.172	Normal cervix	1,025	0.013	Sigmoid tumor	9,073	0.117	Normal sigmoid	3,185	0.041	Tissue	μc./Gm.	Liver	0.17	Fascia, above umbilicus	0.04	Tumor, necrotic	0.14	Muscle, rectus	0.02	Tumor retroperitoneal node	0.11	Tumor retroperitoneal node	0.13	Fat, from colon	0.10	Abdominal fluid	0.04	Subcutaneous tissue	0.02	Skin	0.05
Tissue	cts./Gm.	μc./Gm.																																										
Cervical tumor	13,400	0.172																																										
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Skin	0.05																																											

TABLE XIV: (Continued)

Case, Sex, and Age	Diagnosis	Ga ⁷² in mc.	Per cent Excreted	Evidence of Concentration in Tumor			Additional Data and Remarks
				External Measurement	Autopsy	Biopsy	
G.E.C. 010033 ♂44	Lymphosarcoma	(a) 22.2	14.8	N.D.	Autopsy but no gallium assay	0	Biopsy twenty-four hours after 22 mc. Ga ⁷² Tissue $\mu\text{c./Gm.}$ Chest fluid 0.051 Skin 0.102 Muscle 0.030 Lymph node 0.089 Lymph node 0.081 Autopsy five months later, with Au ¹⁹⁹ distribution study
J.D.L. 010034 ♂18	Reticulum-cell sarcoma	(a) 2.6	0.27	N.D.	Autopsy but no gallium assay	N.D.	Studied chiefly with P ³² . Autopsy with P ³² distribution study
P.J.F. 010036 ♂34	Sarcoma of ischium and thigh	(a) 22.0 (b) 23.5	12.8 14.9	0	N.D.	+	Biopsy twenty-four hours after 22 mc. Ga ⁷² Tissue cts./Gm. $\mu\text{c./Gm.}$ Tumor 84,600 1.040 Muscle 232 0.003 Tumor 5,725 0.070
F.H. 010040 ♀61	Carcinoma of urinary bladder	(a) 1.3	4.6	N.D.	N.D.	N.D.	Studied chiefly with Au ¹⁹⁹ . Death at home. No autopsy
M.L.H. 010041 ♀37	Plasma-cell myeloma	(a) 1.3 (b) 23.0	2.5 12.4	N.D.	+	+	Biopsy twenty-four hours after 23 mc. Ga ⁷² Tissue $\mu\text{c./Gm.}$ Skin scar 0.05 Fat, subcutaneous 0.03 Tumor 0.14 Tumor 0.48 Vertebra with tumor 0.80 Vertebra without tumor 0.53 Normal skin 0.05
O.D. 010042 ♂40	Plasma-cell myeloma	(a) 1.0 (b) 20.8	1.2 12.5	0	N.D.	N.D.	Disease still responding to conventional therapy
P.E. 010050 ♂43	Plasma-cell myeloma	(a) 0.7 (b) 21.2	20.5 63.4	0	N.D.	N.D.	Patient not treated here. Discharged after the two tracer doses of gallium
N.M. 110060 ♀51	Hodgkin's disease	(a) 19.9	59.4	N.D.	Autopsy but no gallium assay	+	Biopsy twenty-four hours following 20 mc. Ga ⁷² Tissue $\mu\text{c./Gm.}$ Tumor from neck 1.627 Muscle 0.113 Death one month after biopsy. Autopsy
C.L.C. 110064 ♂49	Small-cell sarcoma (Ewing's tumor) of sacrum	(a) 20.5	60.5	N.D.	0	0	Biopsy of lung after 20.5 mc. Ga ⁷² Tissue $\mu\text{c./Gm.}$ Tumor 0.12 0.10 0.10 Lung 0.16 Rib 0.36 Muscle 0.02 Plasma 0.13 Skin 0.10 Sudden death from pulmonary embolus one day after uneventful lung biopsy. Autopsy assays showed no significant concentration of gallium in tumor
W.B. 110065 ♂26	Hodgkin's disease	(a) 2.2 (b) 21.4	28.4 71.1	N.D.	N.D.	N.D.	Patient admitted for trial of gallium treatment but, after evaluation, it was decided that x-ray therapy would give him a better chance of improvement, and this has been the treatment.

TABLE XIV: (Continued)

Case, Sex, and Age	Diagnosis	Ga ⁷² in mc.	Per cent Excreted	Evidence of Concentration in Tumor			Additional Data and Remarks
				External Measurement	Autopsy	Biopsy	
L.S. 110068 ♀56	Plasma-cell myeloma	(a) 1.8 (b) 20.6	19.0 60.1	N.D.	Autopsy; no assay data	N.D.	Rib biopsy forty-five hours after 20.6 mc. Ga ⁷² Tissue $\mu\text{c./Gm.}$ Rib 0.56 Subcutaneous 0.09 Skin 0.11 Muscle 0.09 Plasma 0.21 Patient died suddenly. Autopsy. No tissue assay for radioactivity
G.H. 110071 ♂67	Chronic lymphocytic leukemia	(a) 22.0	53.4	N.D.	N.D.	0	Biopsy (lymph node) forty-eight hours after 22 mc. of Ga ⁷² Tissue $\mu\text{c./Gm.}$ Lymph node 0.11 Plasma 0.33 W B C 0.04 R B C 0.09 Patient discharged after this bi- opsy study. X-ray therapy advised
C.I. 110074 ♂48	Plasma-cell myeloma	(a) 1.5 (b) 20.5	6.3 41.2	N.D.	N.D.	0	Biopsy of involved rib forty-eight hours after 20.5 mc. Ga ⁷² Tissue $\mu\text{c./Gm.}$ Rib 0.98 Muscle 0.09 Skin and subcutaneous tissue 0.14 Patient treated with x-rays and P ³² . In fair condition five months following biopsy
R.P. 110076 ♂19	Giant-cell tumor of bone involving sa- crum	(a) 2.8 (b) 22.4 (c) 58.7	13.2 51.7 58.7	0	N.D.	See assays	Biopsy forty-eight hours after 20.4 mc. Ga ⁷² Tissue $\mu\text{c./Gm.}$ Soft tumor 0.32 Bone and cartilage 0.04 Thin layer of bone adja- cent to tumor 2.21 Bone and tumor 1.67 Muscle 0.05 Skin 0.04 Plasma 0.18 RBC 0.04 Patient discharged for treatment elsewhere
E.E.N. 110083 ♂70	Carcinoma of prostate with extensive me- tastases	(a) 1.6 (b) 50.0	11.3 Death soon after 2nd dose	N.D.	+	N.D.	Patient, admitted in terminal con- dition, given Ga ⁷² and P ³² simul- taneously for autogram studies at various stages of decay. Death five hours after admin- istration of the two isotopes. Tissue assays for both isotopes
H.L. 110094 ♀34	Reticulum-cell sarcoma	(a) 21.9 (b) 17.8 (c) 21.2	53.6 48.8 65.8	+	N.D.	+	Biopsy of breast lesion forty-eight hours after 21.9 mc. Ga ⁷² Tissue $\mu\text{c./Gm.}$ Tumor 0.57 Skin 0.11 Fat 0.20 Plasma 0.20 RBC 0.07 Biopsy of right ilium forty-eight hours after 21.2 mc. Ga ⁷² Tissue $\mu\text{c./Gm.}$ Bone with tumor 2.20 Bone with less tumor 1.39

TABLE XIV: (Continued)

Case, Sex, and Age	Diagnosis	Ga ⁷² in mc.	Per cent Excreted	Evidence of Concentration in Tumor			Additional Data and Remarks																				
				External Measurement	Autopsy	Biopsy																					
							Normal cortical bone 0.66 Muscle 0.04 Skin 0.17 Plasma 0.22 RBC 0.05 Patient discharged, x-ray therapy advised here, given near her home. Feeling fairly well thr and a half months following biopsy																				
J.W.M. 110099 ♂40	Plasma-cell myeloma	(a) 2.4 (b) 21.5	9.1 39.9	0	N.D.	N.D.	Patient discharged after excretion study and external counting study had been done and after he had been started on urethane Biopsy of abdominal mass and ribs forty-eight hours after 21.5 mc. Ga ⁷²																				
W.R.M. 110101 ♂50	Plasma-cell myeloma	(a) 1.6 (b) 21.5	52.5 47.5	N.D.	N.D.	+	<table><tr><th>Tissue</th><th>μc./Gm.</th></tr><tr><td>Bone with ? tumor</td><td>0.87</td></tr><tr><td>Solid tumor</td><td>6.03</td></tr><tr><td>Bone with fibrosis</td><td>9.9</td></tr><tr><td>Bone with tumor</td><td>11.63</td></tr><tr><td>Muscle</td><td>0.06</td></tr><tr><td>Skin</td><td>0.10</td></tr><tr><td>Fat</td><td>0.03, 0.02</td></tr><tr><td>Plasma</td><td>0.19</td></tr><tr><td>RBC</td><td>0.04</td></tr></table> Patient discharged on urethane, to continue under care of his per- sonal physician	Tissue	μc./Gm.	Bone with ? tumor	0.87	Solid tumor	6.03	Bone with fibrosis	9.9	Bone with tumor	11.63	Muscle	0.06	Skin	0.10	Fat	0.03, 0.02	Plasma	0.19	RBC	0.04
Tissue	μc./Gm.																										
Bone with ? tumor	0.87																										
Solid tumor	6.03																										
Bone with fibrosis	9.9																										
Bone with tumor	11.63																										
Muscle	0.06																										
Skin	0.10																										
Fat	0.03, 0.02																										
Plasma	0.19																										
RBC	0.04																										
O.M. 110110 ♂47	Chronic osteomyelitis ? Squamous-cell car- cinoma at site of in- flammation	(a) 20.3	57.7	N.D.	N.D.	See assay data	No definite diagnosis of neoplasm. Biopsy forty-eight hours after 20.3 mc. Ga ⁷² <table><tr><th>Tissue</th><th>μc./Gm.</th></tr><tr><td>Granulation tissue and epithelium (2 samples)</td><td>0.18, 0.13</td></tr><tr><td>Epithelial, granulation tissue and bone spicules</td><td>0.51</td></tr><tr><td>Fat and subcutaneous tissue</td><td>0.42</td></tr><tr><td>Bone with epithelial and inflammatory tissue</td><td>0.92</td></tr><tr><td>Skin (normal)</td><td>0.14</td></tr><tr><td>Muscle</td><td>0.10</td></tr><tr><td>Plasma</td><td>0.21</td></tr><tr><td>RBC</td><td>0.05</td></tr></table> Patient discharged. Advised to have care elsewhere for osteo- myelitis. We could not decide surely about the malignancy of the hyperplastic epithelium near the draining sinus	Tissue	μc./Gm.	Granulation tissue and epithelium (2 samples)	0.18, 0.13	Epithelial, granulation tissue and bone spicules	0.51	Fat and subcutaneous tissue	0.42	Bone with epithelial and inflammatory tissue	0.92	Skin (normal)	0.14	Muscle	0.10	Plasma	0.21	RBC	0.05		
Tissue	μc./Gm.																										
Granulation tissue and epithelium (2 samples)	0.18, 0.13																										
Epithelial, granulation tissue and bone spicules	0.51																										
Fat and subcutaneous tissue	0.42																										
Bone with epithelial and inflammatory tissue	0.92																										
Skin (normal)	0.14																										
Muscle	0.10																										
Plasma	0.21																										
RBC	0.05																										
E.M. 110111 ♂34	Round-cell sarcoma (Ewing's group) aris- ing in os calcis	(a) 20.4	60.2	Slight evi- dence of concentra- tion in one bone le- sion	N.D.	0	Biopsy forty-five hours after 20.4 mc. Ga ⁷² <table><tr><th>Tissue</th><th>μc./Gm.</th></tr><tr><td>Bone and tumor of ilium (3 samples)</td><td>0.72, 0.59, 0.97</td></tr><tr><td>Normal bone</td><td>0.99</td></tr><tr><td>Muscle</td><td>0.01</td></tr><tr><td>Skin</td><td>0.04</td></tr><tr><td>Fat</td><td>0.03</td></tr><tr><td>Plasma</td><td>0.07</td></tr><tr><td>RBC</td><td>0.04</td></tr></table>	Tissue	μc./Gm.	Bone and tumor of ilium (3 samples)	0.72, 0.59, 0.97	Normal bone	0.99	Muscle	0.01	Skin	0.04	Fat	0.03	Plasma	0.07	RBC	0.04				
Tissue	μc./Gm.																										
Bone and tumor of ilium (3 samples)	0.72, 0.59, 0.97																										
Normal bone	0.99																										
Muscle	0.01																										
Skin	0.04																										
Fat	0.03																										
Plasma	0.07																										
RBC	0.04																										

TABLE XIV: (Continued)

Case, Sex, and Age	Diagnosis	Ga ⁷² in mc.	Per cent Excreted	Evidence of Concentration in Tumor			Additional Data and Remarks																
				External Measurement	Autopsy	Biopsy																	
A.B. 110113 ♀ 43	Carcinoma of cervix with skeletal metas- tases	(a) 1.2	7.2	0	N.D.	N.D.	Patient discharged soon after test doses of gallium. X-ray therapy advised																
		(b) 19.1	18.9																				
R.M. 110116 ♀ 66	Plasma-cell myeloma	(a) 1.1	10.1	N.D.	N.D.	+	Biopsy forty-eight hours after 21.2 mc. Ga ⁷²																
		(b) 21.2	55.1																				
							<table><tr><th>Tissue</th><th>mc./Gm.</th></tr><tr><td>Skin</td><td>0.24</td></tr><tr><td>Subcutaneous tissue</td><td>0.05</td></tr><tr><td>Muscle</td><td>0.05</td></tr><tr><td>Involved rib with marrow</td><td>1.94</td></tr><tr><td>Involved rib without marrow</td><td>1.34</td></tr><tr><td>Plasma</td><td>0.46</td></tr><tr><td>RBC</td><td>0.12</td></tr></table>	Tissue	mc./Gm.	Skin	0.24	Subcutaneous tissue	0.05	Muscle	0.05	Involved rib with marrow	1.94	Involved rib without marrow	1.34	Plasma	0.46	RBC	0.12
Tissue	mc./Gm.																						
Skin	0.24																						
Subcutaneous tissue	0.05																						
Muscle	0.05																						
Involved rib with marrow	1.94																						
Involved rib without marrow	1.34																						
Plasma	0.46																						
RBC	0.12																						
							Patient subsequently treated with cortisone and urethane.																
A.A 110117 ♀ 56	Plasma-cell myeloma	(a) 0.93	10.9	N.D.	0	N.D.	Patient admitted in terminal con- dition. Death soon after last dose of Ga ⁷² . Autopsy assays showed unusually high levels in kidney																
		(b) 21.2	54.3																				
		(c) 16.6	19.9																				
		(d) 5.7	11.7																				
		(Some lost) (Died soon after dose)																					

11-2-50: A film of the chest made on re-admission showed the nodule to be approximately 2.5 cm. in diameter, definitely smaller than one month previously. The pneumothorax and effusion previously described were not seen on this film.

Course: On Aug. 4, 1950, the patient was given 0.9 mc. of Ga⁷². Excretion and external counting studies were made. These were repeated on Aug. 10, 1950, following an additional 1 mc. dose of Ga⁷². The external counting studies with a highly collimated Geiger-Müller tube were unsuccessful in demonstrating localized uptake of activity in the tumor nodule over the left chest, and survey study was unsuccessful in revealing any other areas of significant selective uptake of activity.

It was believed that the lesion was probably inoperable, because of the pleural fluid and pneumothorax, indicating probable pleural extension and perhaps implantation, and also because of the probability of multiple metastases not visualized roentgenographically rather than the single one shown on the film. It was decided, however, that if following the therapeutic trial of Ga⁷² no significant changes had occurred, an exploratory thoracotomy would be attempted and the lesion resected if possible.

The patient was given doses of Ga⁷² ranging from 20 to 78 mc. at approximately three- or four-day intervals until Sept. 25, 1950. At this time he had received a total of 578 mc. During the course of large doses of Ga⁷², he manifested anorexia ranging from moderate to severe, with associated nausea and vomiting. Peripheral blood examinations revealed a decided drop in the white blood cell count to a low of 650 on Aug. 4, 1950, while the hemoglobin dropped to a level of 8.6 gm. on that date. The weight on

admission was 175 pounds; on Oct. 9, it was 158 pounds. There were no manifestations of skin eruption, jaundice, or urinary abnormalities. The patient was discharged on Oct. 21, 1950, and returned to his home. During his stay there, he suffered no untoward complications. He was readmitted on Nov. 1, 1950. He was given 26 mc. of Ga⁷² on Nov. 2, 1950, and twenty-four hours later an exploratory thoracotomy was done.

The operation was performed by Dr. R. W. Postlethwait, of the Medical College of South Carolina. No pleural implants could be found. There was one nodule about 3 cm. in diameter in the interlobar fissure, partially in the lingula of the upper lobe. A second, but much smaller nodule, about 4 or 5 mm. in diameter, was present in the upper lobe. The hilus showed no evidence of extension of the disease. It was decided that a pneumonectomy should be done, and this was accomplished without difficulty.

Gross examination of the resected lung showed the larger nodule to be well below the pleural surface. This lesion consisted of an irregular zone of fibrosis within which was a dark red, firm blood clot. Two other similar but smaller lesions were also present. On histologic section the nodules were found to consist of a zone of hemorrhage and necrosis.

There were numerous hemosiderin-laden phagocytes throughout. The periphery was made up of proliferating capillaries and fibrocytes. Of real interest was the presence of several giant nuclei which were mono- or multinucleated, in the so-called capsule. These had a hyperchromatic appearance, with clumped chromatin and criteria sufficient to designate them as malignant cells.

The patient had a relatively uneventful postopera-

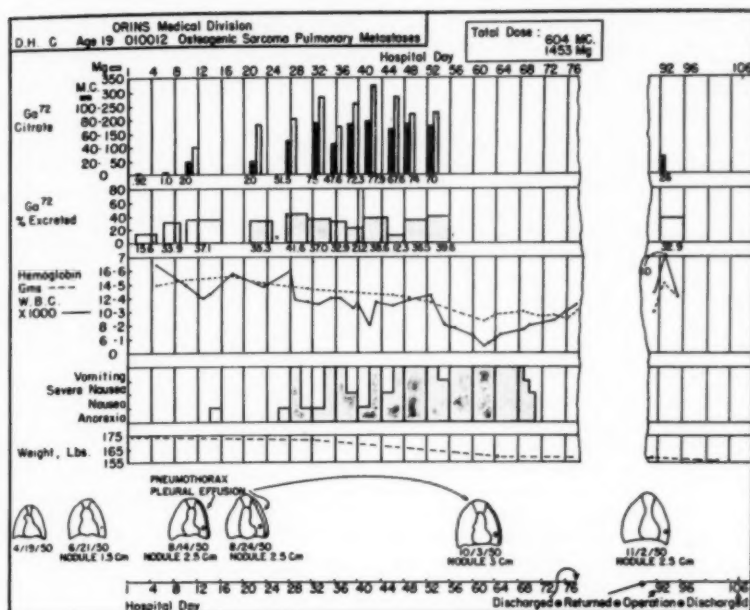


Fig. 17. Summary of Case No. 010012.

tive course and was finally discharged on Nov. 17, 1950, to return to his home. Hematology values were normal.

Comment: This patient was thought to have typical pulmonary metastases from a primary osteogenic sarcoma. He received a large course of gallium⁷², following which a pulmonary nodule, thought to be metastatic, first increased and then decreased in size. The lesions which were removed at pneumonectomy, instead of being typical metastases, were not characteristic of any specific lesion. Specific studies in reference to tuberculosis failed to bring out any supporting evidence for that disease. There seemed to be three possible explanations for the pulmonary lesions:

1. They may have represented pulmonary metastases of osteogenic sarcoma, which underwent spontaneous infarction for some reason.

2. They may have been pulmonary metastases of osteogenic sarcoma, which underwent necrosis because of treatment with radioactive gallium. If so, this is the only example of such an effect in the series,

where there were many opportunities for it to occur.

3. These lesions may represent a pulmonary disease entirely unrelated to the primary osteogenic sarcoma, such as some form of chronic infectious granuloma or healing abscess due to aspiration. The serial chest films were much more compatible with the diagnosis of neoplasm.

CASE III: History: W. R. C. (No. 110088), a 27-year-old white male, was admitted in June 1951. A mass in the right leg had appeared in 1947. A supracondylar amputation was done in July 1950. The histologic diagnosis was fibrosarcoma. There was x-ray evidence of pulmonary metastases in June 1951. The patient had been asymptomatic and had not received any x-ray therapy.

Physical Examination: Temperature 37.2° C., pulse 92, respirations 20, blood pressure 145/100. The patient was moderately overweight, alert, and ambulatory with the aid of a prosthesis. Examination revealed no abnormality except for the absence of the right leg.

X-Ray Studies: On June 28, 1951, roentgenograms showed multiple nodular areas of increased density scattered throughout both lung fields. A complete bone survey showed no evidence of metastatic bone lesions. On Aug. 6, 1951, the x-ray findings were unchanged.

Course: The patient was given 2.1 mc. of Ga^{72} intravenously on June 21, followed by external counting with a collimated Geiger tube twenty-four hours later, which revealed no localized areas of increased uptake. He was given stable gallium citrate intravenously with only tracer amounts of Ga^{72} twice weekly from June 21 through August 6. Approximately 250 mg. of stable gallium was given with each infusion, so that he received a total of 2,785 mg. or 35.8 mg./kg. The total Ga^{72} received was 13.7 mc. The stable gallium given equaled that administered as carrier to those patients who received Ga^{72} in large therapeutic amounts. There were some anorexia and occasional nausea toward the latter part of the treatment. Fever and a sore throat with ulcerated lesions on pharynx and gums developed midway through the course of gallium. Similar lesions had occurred on several occasions in the past. Fever and mouth lesions lasted about a week and disappeared under treatment with Aureomycin. The patient lost about 12 pounds of weight, but at the time of discharge, Aug. 17, 1951, his appetite was improving steadily. The eighteen-hour urine concentration test showed some change in that he was able to concentrate to 1.025 on June 21, but to 1.011 only on Aug. 16. On one occasion, July 18, there was +++ albuminuria, but none after that time; PSP renal function test, on Aug. 17, showed excretion of 42 per cent in one hour and 28 per cent in the second hour; non-protein nitrogen was not elevated.

At home, the patient's general strength improved, and he felt as well as before receiving the stable gallium. He had no cough or chest pain and his appetite was good. X-ray examination of the chest, in October 1951, showed that the pulmonary metastases had increased in size.

Laboratory Findings: Hematologic studies before administration of gallium (June 1951), those of Aug. 13, eleven days after the last injection of gallium, showing anemia and slight depression of lymphocytes, and those of Oct. 1, two months after gallium administration, were as shown on the next page.

Comment: This patient was given stable gallium citrate intravenously with only tracer amounts of Ga^{72} , in order to determine the toxic effects of the metal alone. The tracer amounts of Ga^{72} were given in order to obtain data on excretion. Toxic effects noted were (1) skin rash, (2) anorexia, (3) albuminuria on two occasions, and (4) decreased kidney function by concentration test. Because of a viral gingivostomatitis occurring during the middle of the course of gallium and lasting about a week, it was difficult to evaluate the gallium effects during that period. Nausea developed only twice. There was mild

fluctuating depression of the white cell count and a definite depression of red cells. Thrombocytes were not affected.

DISCUSSION

The patterns of gallium localization were well demonstrated, especially in autoradiographic records, but the metabolic factors responsible for these localizations are not known. In normal bone the gallium was found to be just beneath the periosteum in a fine line. In growing bones, there was a striking local deposition at the epiphyseal lines. The lesions of osteogenic sarcoma showed great ability selectively to withdraw the gallium from blood. The distribution in these lesions was very uneven and could not be well correlated with any particular morphologic characteristic of the tumor. Two areas of the same lesion which appeared identical under the microscope sometimes showed a great difference in gallium content. However, there was a very pronounced tendency for the isotope to concentrate in and near areas of calcification in these lesions. Destructive lesions of bones showed a generally low concentration of gallium in their central areas, but sometimes a prominent deposition at areas where the neoplasm was invading normal bone. Thus there seemed to be a distinct tendency for the gallium to localize in areas of bone activity either osteoblastic or osteolytic.

Fairly high levels of radioactivity were seen in the normal liver, spleen, and bone marrow. It may be that this was in part related to the formation in the blood of a gallium colloid which was taken out by reticulo-endothelial cells. However, there is no evidence as yet for the existence of such a colloidal form of the isotope, and the facts that rather large amounts were excreted in the urine and that the kidneys and endocrine glands showed high levels of activity are somewhat against this hypothesis. Highly cellular soft-tissue tumors which showed no tendency to calcify sometimes had fairly high concentrations of the isotope, suggesting that it may be involved in nucleoprotein metabolism.

Case No. 110088	June 1951	Aug. 13, 1951	Oct. 1, 1951
R.B.C.	6.10 million	3.88 million	5.85 million
Hemoglobin	16.5 gm.	10.6 gm.	13.9 gm.
Hematocrit	52%	32%	46%
Mean Corpuscular Volume	85	82	79
Mean Corpuscular Hemoglobin	27	26	24
Mean Corpuscular Hemoglobin Concentration	32	31	30
W.B.C.	6,650	5,500	5,750
Sedimentation rate	12 mm. in 1 hour (uncorrected)	20 mm. in 1 hour (corrected)	5 mm. in 1 hour (corrected)
Differential Count			
Myelocytes			0.5
Metamyelocytes			0.5
Band neutrophils	1.0	10	2.5
Segmented	51.5	54.5	45
Lymphocytes	31.5	15	30
Monocytes	9.0	16.5	4.5
Eosinophils	6.5	3.5	13.5
Basophils	0.5	0.5	2.5
Atypical cells (resembling lymphoid plasma cells)			1
Thrombocytes	Normal	Normal	Normal
"Toxic" granulation	++	++	+
Red cells	Normal	Moderate anisocytosis and poikilocytosis	Mild anisocytosis and poikilocytosis; some anisochromia. Occasional punctate basophilia of red cells. Reticulocytes slightly increased
Bone marrow	A few young lymphocytes Toxic monocytes Cellular, without definite abnormality		Essentially normal cellular marrow
Blood Chemistry			
Acid phosphatase	1.8 King-Armstrong units		0.28 m.m. units
Alkaline phosphatase	8.8 Bodansky units		2.1 Bodansky units
Thymol turbidity	9.4 units		20.8 units
Cephalin cholesterol flocculation	24 hr. 0 48 hr. 0		24 hr. 0 48 hr. ++

Further information about the biochemical factors which influence the distribution of gallium may be forthcoming. If so, it may be possible to reinterpret the data obtained in the present study and to derive information about the nature of tumors involving bone.

As the study progressed, we were impressed with the almost complete lack of any clinical improvement following gallium treatment, even in patients who showed evidence of striking differential localization of gallium in tumor tissue. Most of the patients in whom gallium therapy was at-

tempted were given maximum amounts of the isotope. Only the hopelessness of their prognoses justified a trial of doses so damaging to the hematopoietic tissues. A few evidences of apparent transient symptomatic benefit were seen in individuals with metastatic carcinoma. In one patient there was definite roentgen evidence of recalcification of osteolytic lesions following therapy. Patients with primary bone sarcoma showed no evidence whatever of any slowing of growth of primary or metastatic lesions, and in several cases lesions grew rapidly during high-dosage therapy.

These findings are consistent with the familiar resistance of this neoplasm to conventional x-ray therapy.

In summary, it is our impression that Ga^{72} has been given a thorough clinical

trial in many types of neoplasm involving bone and has been found of no therapeutic value. Gallium may be a valuable element for the study of biochemical and metabolic factors related to bone tumors.

VII. Studies of the Urinary Excretion of Gallium⁷² in Man

H. D. BRUNER, M.D., JOE GRAY, SAMUEL W. ROOT, M.D., and MARSHALL BRUCER, M.D.

Studies of urinary and fecal excretion of the isotope were made routinely. Each patient was assigned an individual bedpan and urinal. Voided urine specimens were transferred to large bottles, and the original container was rinsed with small amounts of water. Collections were made over eight-hour and twenty-four-hour periods, and each total volume, including rinse water, was mixed, measured, and an aliquot was taken for radioassay. During the first few months of the study, separate eight-hour collections were made during the

first three days after administration and twenty-four-hour collections subsequently as long as measurable activity remained or until the next dose was given. Since the major excretion was found to occur during the first twenty-four-hour period, eight-hour collections were not continued beyond the first day. Early studies showed minute fecal excretion of gallium⁷² and fecal excretion studies were discontinued. Table XIV (Section VI) lists the detailed urinary excretion data obtained from some of the patients.

TABLE XV: STUDIES OF THE URINARY EXCRETION OF Ga^{72} IN MAN
("Tracer" dose of about 1 mc.)

Patient No.	Diagnosis	Dose (mc.)	Date	Per Cent of Dose Excreted						Remarks	
				First Day (in 8 hr. periods)			Second Day	Third Day	Fourth Day		Total
				1st	2nd	3rd					
7	Multiple myeloma	1.00	7/31	*	*	1.0	*	*		4.0	
13	Multiple myeloma	0.92	8/4	13.0	5.0	5.0	6.0	3.0	2.0	34.0	
18	Multiple myeloma	1.00	8/31	13.0	10.0	5.0	24.0	3.0		55.0	
16	Osteogenic sarcoma	1.00	8/18	18.0		3.0	3.0	2.0		26.0	Pre-Vit. D†
16	Osteogenic sarcoma	1.00	8/28	22.0		19.0	8.0			49.0	Post-Vit. D
14	Osteogenic sarcoma	1.00	8/7	2.0	8.0	3.0	5.0	2.0		20.0	
9	Osteogenic sarcoma	1.00	7/31	8.0	3.0	2.0	6.0	2.0		21.0	
8	Osteogenic sarcoma	1.00	7/31	8.0	3.0	2.0	6.0	2.0	2.0	23.0	Pre-Vit. D†
8	Osteogenic sarcoma	1.00	8/7	6.0	5.0	2.0	5.0	2.0		20.0	Post-Vit. D
12	Osteogenic sarcoma	0.92	8/4	10.0		8.0	5.0	3.0		26.0	Pre-Vit. D†
12	Osteogenic sarcoma	1.00	8/10	22.0	14.0	1.0	13.0	5.0		55.0	Post-Vit. D
19	Osteogenic sarcoma	2.30	9/5	13.0	3.0	3.0	3.0	5.0		27.0	Pre-Vit. D†
19	Osteogenic sarcoma	1.91	9/11	Less than 1% Total Excretion‡							Post-Vit. D
23	Osteogenic sarcoma	1.91	9/11	19.0	13.0	5.0	5.0	3.0		45.0	Pre-Vit. D†
23	Osteogenic sarcoma	1.00	9/18	13.0	5.0	2.0	2.0	2.0		24.0	Post-Vit. D
4	Metastatic thyroid carcinoma	1.00	7/17	10.0	3.0	6.0	10.0	5.0	6.0	40.0	
6	Metastatic thyroid carcinoma	1.00	7/31	5.0	5.0	2.0	5.0	2.0		19.0	
11	Chronic myelogenous leukemia	1.84	8/4	5.0	Lost	6.0	3.0	2.0	1.0	17.0	
17	Hodgkin's disease	1.00	8/25	13.0	3.0	2.0	3.0	2.0		23.0	
21	Chronic lymphatic leukemia	1.60	9/7	24.0	8.0	2.0	2.0	5.0	2.0	43.0	
20	Lymphosarcoma	1.60	9/7	5.0	5.0	2.0	3.0	1.0	1.0	17.0	

* Less than 1%.

† Prior to and after a weeks course of 150,000 I.U. of concentrated Vit. D, t.i.d.

‡ Probably due to injection in subcutaneous tissue.

TABLE XVI: STUDIES OF THE URINARY EXCRETION OF GALLIUM IN MAN
(Doses larger than 1 mc.)

Patient No.	Date	Diagnosis	Dose				Per Cent Excreted of Initial Dose						
			Mc. Ga ⁷³	Mc./- kg.	Mg. Ga	Mg./- Kg.	First Day (in 8 hr. periods)			Second Day	Third Day	Fourth Day	Total
							1st	2nd	3rd				
7	8/4	Multiple myeloma	8.8	0.16	50	1.0	3	2	3	3	2		13
	8/7		8.4	0.15	88	1.4	3	2	3	4	2		14
	8/10		8.0	0.14	103	1.9	2	5	3	5	2	2	19
	8/14		10.0	0.17	50	1.0	5	2	3	5	2	2	19
	8/18		8.7	0.16	68	1.2	5	3	2	5	3		18
	8/21		9.4	0.17	75	1.4	5	6	3	5	1	1	21
	8/25		9.0	0.16	86	1.4	5	2	8	6	2		23
	8/28		8.0	0.14	43	0.8	11	5		3			19
	8/31		14.9	0.27	53	1.0	3	6	1	6	2		18
	9/5		12.3	0.23	39	0.7	11	3	3	5			22
	9/11		49.9	0.92	166	3.1	10		6	5	2		23
			147.4	2.51	821	14.9							
	13	8/28	Multiple myeloma	20.0	0.34	107	1.8	19	6	3	6	3	
8/31		40.0		0.69	153	2.6	21	11	5	6	3	3	49
9/5		52.7		0.91	184	3.2	23	6	3	6			38
9/7		44.7		0.77	173	3.0	25	11	2	6	3	1	48
9/11		20.6		0.36	64	1.1	Less than 1 per cent excreted by time of death fifty-five hours post-injection						
		178.0		3.07	681	11.7							
18	9/5	Multiple myeloma	23.5	0.57	78	1.9	19	11	6	5			41
	9/7		20.3	0.50	80	1.9	6	3	2	10	3	1	25
			43.8	1.07	158	3.8							
17	8/20	Hodgkin's disease	20.0	0.34	107	1.8	29	5	1	4	2	1	42
	8/31		51.5	0.83	200	3.3	35	5	5	3			48
			71.5	1.17	307	5.1							
9	8/7	Osteogenic sarcoma	19.6	0.30	150	2.30	37	3	6	5	2		53
	8/10		28.6	0.44	250	3.85	42	8		5	2	1	58
	8/14		50.0	0.80	250	3.85	40	6	3	6	1		56
	8/22		37.6	0.58	300	4.60	38	5	6	5	1		55
	8/25		32.0	0.50	300	4.60	42		8	3	1		54
	8/28		20.0	0.30	107	1.65	35	10	2	5	1	2	55
	8/31		51.5	0.80	200	3.08	38	8	2	3	1		52
			239.3	3.72	1,557	23.93							
8	8/10	Osteogenic sarcoma	21.3	0.32	170	2.54	27	19	3	4	2	1	56
	8/14		50.0	0.75	250	3.73	46	10	3	5	2	1	67
	8/23		28.3	0.42	300	4.48	51	6	3	5	2		67
	8/28		50.0	0.75	270	4.03	48	6	2	4			60
	8/31		51.5	0.77	200	2.98	45	8	5	5	2	1	66
	9/5		70.6	1.05	271	4.04	42	6	2	3			53
	9/7		66.8	1.00	256	3.82	30	Lost	3	5	2		40
	9/11		92.8	1.38	342	5.10	37	6	5	5			53
			431.3	6.44	2,059	30.72							
12	8/14	Osteogenic sarcoma	20.0	0.30	100	1.50	34	10	5	11	1	2	63
	8/25		20.0	0.30	190	2.64	46	5	2	4	2		59
	8/31		51.5	0.72	200	2.78	50	8	3	3	2		66
	9/5		77.7	1.07	270	3.75	46	6	3	3			58
	9/7		47.6	0.66	157	2.18	37	8	5	2	2		54
	9/11		72.3	1.00	258	3.58	24		5	2	2		33
			289.1	4.05	1,175	16.43							
16	8/31	Osteogenic sarcoma	27.5	0.86	90	2.81	37		5	2	3		47
	9/5		52.0	1.62	84	5.75	34		3	3			40
	9/7		46.3	1.45	179	5.59	32	2	3	3	6		46
	9/11		49.0	1.53	166	5.19	30	3		3	3		39
			174.8	5.46	519	19.34							

From excretion data some general conclusions may be drawn. Individual doses ranged from about 1 mc. (4.7 to 5.2 mg.) up to about 77 mc.

1. In general there was a tendency for higher doses to be associated with a higher excretion of gallium in man. This is similar to the excretion pattern observed in detailed studies of the rat.

2. Although a higher proportion of the metal was excreted with higher doses, the absolute amount of retention of metal was far greater with higher doses.

3. In some patients there was a tendency for much greater retention of metal, regardless of dose, than in other patients.

This fact could not be correlated with the disease or other data.

4. No relationship was demonstrated between the sequence of doses. A build-up of the metal retained within the body did not affect the excretion of succeeding doses.

5. There was no evidence in the urine of damage to the genitourinary tract due to the passage through the kidney of large amounts of either metal or radiation. Such damage did occur and was an outstanding feature of the toxicity picture in dogs. It was completely absent in man.

Tables XV and XVI show urinary excretion data for patients receiving about 1 mc. and larger doses, respectively.

VIII. Autopsy Studies of Distribution of Gallium⁷²

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ERRORS INHERENT IN AUTOPSY MEASUREMENTS

In Table XVII there is listed the *differential absorption ratio to heart* of Ga⁷² as it was retained in patients coming to autopsy. It is difficult to interpret these autopsy data since many errors are cumulative. The dosages and time of death could not be planned. The tissues were not perfused. The short half-life demanded rapid measurement, and with many samples to be counted, some with very low concentration, a simple measuring system had to be used.

Only small pieces of organs were measured. When a number of samples from the same organ were measured, the variation from sample to sample was considerable. This is not due to an error of measurement but represents a true variation in deposition within the organ. In measuring any of the gross autoradiograms of slices of tissue, it is easy to see how two 0.5-gm. samples could be selected from adjacent areas of the same tissue and give widely different results. In patient 010003, the lowest and the highest tumor assays from samples taken from the same metastasis read 13

and 254, different by a factor of 20. In another study, of samples selected from an autoradiogram in which one piece of tissue was taken from the area of least photographic exposure and one from the area of most photographic exposure, variations by a factor of 100 were demonstrated.

In a series of studies on adjacent samples taken from the femur, the areas were selected after looking at a thin-slice autoradiogram of the bone. The following are the measurements for 4 of 26 areas:

Area of Bone	Corrected Counts per minute per gram
Cortical bone	2.8×10^4
Trabecular marrow	7.4×10^4
Epiphyseal line	1.5×10^5
Subperiosteum	7.4×10^5

These thin-slice autograms range from 2 to 5 mm. thick, which is large in terms of the range of beta particles. When even thinner slices are prepared, the variation becomes more pronounced.

Another major error follows from the fact that all of these patients were in a rapidly developing terminal state. The distribution of the last dose of Ga⁷² may have little

TABLE XVII: RADIOASSAY OF TISSUES FOLLOWING AUTOPSY OF THIRTEEN PATIENTS WHO RECEIVED Ga⁷²
Differential Absorption Ratio to Heart

Patient	110054	110061	110083	110073	110117	010023	010003	010013	010016	010041	110079	010049	110064
Last dose of Ga ⁷² (mc.)	0.5	21.3	47.5	21.3	5.7	36.0	13.0	20.6	17.3	22.0	3.6	15.9	20.5
Time last dose to death hour	1.5	5	5	6	7	15	15	30	40	44	51	77	32
Disease	Prostate	Osteo	Prostate	Osteo	Plasmo	Osteo	Osteo	Plasmo	Osteo	Plasmo	Breast	Kidney	Ewing's
Heart	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0*
Plasma	8.2	1.3	2.0	2.1	2.9	†			1.1	3.0	0.4	0.1	4.0
Skin		3.4	5.7	3.7	3.8	3.2	1.7	2.9	1.5	4.0	2.0	1.7	3.5
Muscle		0.6	1.3	0.8	0.7	0.8	1.1	0.7	0.3	1.0	0.9	0.8	0.0
Fat		1.7	0.8	1.0	0.6				0.2	1.0			0.0
Liver	1.3	3.1	3.2		11.3	8.5	8.8	6.9	9.2	20.0	4.9	7.2	48.0
Bile	0.2	1.1		2.1		0.1	2.5	3.3		16.0	4.7	3.0	
Spleen	0.7	2.1	2.3	2.6	4.3	2.4	2.2	7.8	5.9	7.0	4.4	3.4	15.5
Gastrointestinal tract	0.9		37.3			3.6	2.5	2.7	3.6	7.0	1.9	1.7	11.1
Kidney	1.1	18.7	3.9	82.1	227.5	15.1	30.2	6.2	26.7	25.0	39.5	16.2	52.3
Lymph node	2.1	3.9	8.0	3.4			2.9	1.9	1.7	4.0	7.6		34.3
Pancreas	0.8			1.6	2.2	2.4	2.6	1.6	2.5	4.0	2.1	2.7	6.5
Prostate			2.4			1.2		1.2				4.2	4.7
Bladder	0.2			3.1		2.7	4.3	1.6	0.8	49.0	1.4		3.5
Adrenal	0.7	2.0	1.5	2.8	5.7	3.4	2.0	2.4	5.7	9.0	2.3	7.6	81.0
Testis or ovary		1.7					1.8	1.7	1.4			1.8	7.2
Brain	0.1			0.1	0.1		0.7	0.2		1.0		0.3	BG
Pituitary		1.5	2.8	1.2	1.2		1.7	1.8				5.4	8.8
Lung	0.2	1.8	3.4		2.6	2.4	15.6‡	2.8	1.9	6.0	2.0	8.0	17.6‡
Thyroid	1.1	1.5	3.0	1.6	1.7	2.0	1.6	1.2	1.2	3.0		3.1	6.4
Bone cortex		30.1	25.9	51.7	4.4‡	11.6	4.4	11.3‡		23.0‡	20.5		139.0
Bone medulla	0.5	19.5	55.4	43.6	6.4‡	37.8	22.5	5.2‡	27.5	24.0‡	16.1	9.4	41.0
Bone, mixed	0.5	20.2	37.4	30.1		4.5	20.0	7.0‡	21.0	20.0‡	12.4		40.3
Bone cartilage				3.8	4.4	3.7	1.7	4.6	2.8	8.0	4.3	3.4	8.5
Tumor low	1.0	1.6	1.4	1.4		0.5	13.0		1.9	8.0		1.4	0.0
Tumor high	1.8	6.4	3.6	2.5		55.8	253.7		86.5	34.0		10.2	17.4
Tumor in liver	0.4		2.4	2.0							1.5		

* Unreliable count.

† The blank spaces indicate either an unreliable count or no tissue was measured.

‡ Normal tissue mixed with tumor.

BG—Background count

Prostate—Carcinoma of the prostate with metastases to bone.

Osteo—Osteogenic sarcoma with pulmonary metastases.

Breast—Carcinoma of the breast with metastases to bone.

Kidney—Carcinoma of the kidney with metastases to bone.

Plasmo—Malignant plasmocytoma.

Ewing's—Ewing's sarcoma.

or no relation to the distribution of the first dose given weeks earlier. In patients No. 010023 and No. 010013 (Table XVIII), the radiation measurements of the last dose can be compared with measurements of the total accumulation of stable gallium in all doses.

The concentration of stable gallium, although highly influenced by the last dose in some organs, shows a different distribution than that expected from the Ga⁷² tracer on the last dose. In tissues such as skin and brain, where there seems to be an early saturation deposit, the stable and radioactive concentrations are the same. In the kidney, the radioactive dose is in the excretion phase and is higher, as might be expected. The lung appears to accumulate a significant amount of material. The

TABLE XVIII: RELATIVE AMOUNT OF STABLE AND RADIOACTIVE GALLIUM IN TISSUES
(Normalized to Skin Concentration)

Tissue	No. 010023		No. 010013	
	Osteogenic Sarcoma		Malignant Plasmocytoma	
	Ga ⁷²	Stable Ga	Ga ⁷²	Stable Ga
Skin	1.0	1.0	1.0	1.0
Brain	Trace	Trace	0.1	Trace
Liver	2.3	1.9	2.4	13.0
Kidney	4.8	0.6	2.1	0.6
Lung	0.8	1.6	1.0	1.6
Tumor (least)	0.2	2.1	1.0	0.6
Tumor (most)	17.6	16.0	3.3	3.2

liver shows a very high deposition in the plasmocytoma case, very low in the sarcoma case. These differences illustrate the fact that all of the autopsy measurements are of an element in only the early part of its metabolic distribution.

Only one autopsy case is presented in detail, that of patient G. P. (010003).

A 14-year-old white school girl fell in the autumn of 1949 and scraped the skin of the left leg from the ankle to knee. After a few weeks, she noticed pain and swelling over the left mid-thigh. Following a diagnosis and a series of twelve x-ray treatments at a local hospital, she was referred to the Bowman-Gray School of Medicine in March 1950. There, after a biopsy and diagnosis of osteogenic sclerosis sarcoma, a disarticulation of her left leg was done on April 1, 1950. She was discharged on April 13 in good condition. There were no signs of metastases.

admission revealed extensive nodular lesions in both lung fields, with evidence of calcification in some. The left side was almost obliterated, but there was an area of probable tumor with calcification just over the diaphragm.

Figure 18 shows, in summary form, the patient's general course during the thirty-four days of hospitalization. As noted in the general progress notes, there appeared to be a relatively steady and rapid decline after the fifteenth day. This is confirmed by another estimate of general condition—the nurse's estimate of the patient's appetite. Following the fifteenth day there was a marked apathy toward food, with difficulty in eating, and on the twenty-fourth day a tube was inserted in the stomach and

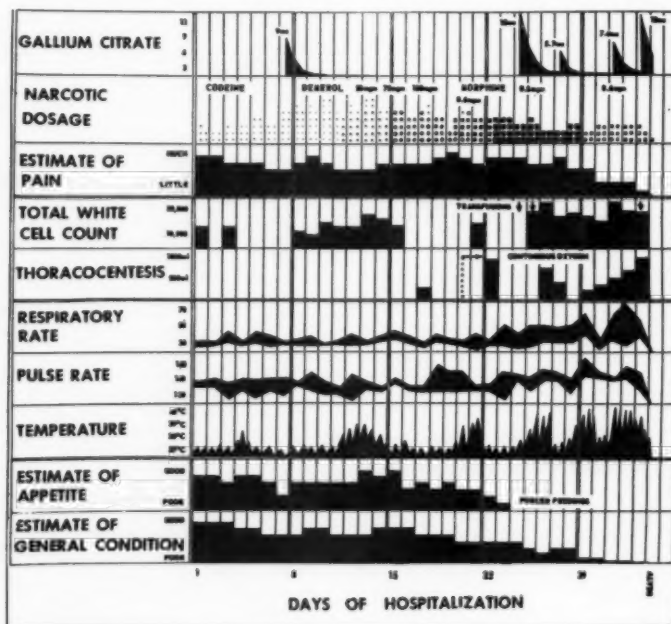


Fig. 18. Summary chart of Case No. 010003.

On May 7, 1950, the patient noticed a tight feeling in the chest, which she described as a deep chest cold. Readmission examination revealed pleural effusion and metastatic lesions in both lungs. It was felt that nothing further could be done with standard therapy and that because of the rapidly growing lesions the patient was a logical candidate for experimental therapy with radiogallium. She was therefore referred to the Medical Division of the Oak Ridge Institute of Nuclear Studies at Oak Ridge.

Upon admission, the patient was in reasonably good condition. Physical examination showed the findings which would be expected in the presence of rapidly growing pulmonary metastases and bilateral pleural effusion. Chest films obtained just prior to

forced feedings were instituted. Pain of increasing severity developed in the region of the left chest. This was not a typically pleuritic sporadic pain but was described as steady and annoying and seemed to be located especially in the posterior left chest wall. There was tenderness to pressure over some areas. The daily estimate of the amount of pain which the patient seemed to experience is shown in Figure 18. Along with this is a record of the narcotics used, their kind, and the number of administrations. The patient was first given codeine, which was replaced by Demerol in increasing dosage. Morphine in 8-mg. doses was started on the nineteenth hospital day and changed to 6-mg. doses on the twenty-ninth day.

About midway during hospitalization a mild

TABLE XIX: EXCRETION OF RADIOGALLIUM INTO PLEURAL FLUID COMPARED WITH LEVELS IN PLASMA WITHDRAWN SIMULTANEOUSLY

Patient G.P. 010003: Osteogenic Sarcoma (Primary Removed) Metastatic to Lungs

Time of Withdrawal of Pleural Fluid	Volume Withdrawn (ml.)	Counts/min./ml. at "0" Time × 10 ³		Approximate* μ c./ml. × 10 ⁻³	
		Pleural Fluid	Plasma	Pleural Fluid	Plasma
After 15 mc. dose 48 hr.	750	3,500	8	9,270	21
After 5.7 mc. dose 9 hr.	425	1,200	5	3,200	13
53 hr.	450	800	1	2,120	0.5
93 hr.	120	60	1	159	0.5
After 7.4 mc. dose 5 hr.	500	2,400	8	6,350	21
22 hr.	550	500	4	1,330	11
32 hr.	625	800	3	2,120	8
47 hr.	750	1,000	1	2,660	0.5

* Measured 1.7 per cent beta counting efficiency.

shortness of breath developed, and it was apparent that pleural fluid was collecting at an increasing rate. A thoracentesis was attempted on the seventeenth hospital day. Only about 150 c.c. of fluid could be obtained. The fluid clotted promptly but incompletely. The sediment showed many red cells but no recognizable neoplastic cells. During the next few days the patient became progressively weaker and more dyspneic. On the twentieth hospital day continuous nasal oxygen therapy was started. Except for a few short periods in a tent, nasal oxygen was continued to death. Weakness and dyspnea were progressive. Pleural effusion developed on the right side. Frequent thoracenteses were attempted. The material withdrawn became more viscous and, especially on the left, seemed to be pocketed in small thick-walled cavities. Because of the rapidly increasing respiratory embarrassment an attempt was made to dissolve the fibrin material with an enzyme preparation supplied by Lederle Laboratories. This preparation contained Streptokinase, 250,000 units, and Streptodornase, 200,000 units. Two ampules were injected on the left side twenty-four hours apart. Beginning on the thirtieth day of hospitalization, within forty-eight hours there was a striking change in character of the pleural fluid. It became possible to withdraw a large amount of hemorrhagic but free flowing fluid. Beginning on about the twenty-ninth day the patient became increasingly moribund. She died early on the thirty-fourth day of hospitalization.

Radiation Data: On the seventh day of hospitalization, a 9-mc. dose of gallium citrate was injected intravenously, preceded by a prophylactic dose of calcium gluconate. This was followed by 15 mc. on the twenty-fourth day, 5.7 mc. on the twenty-seventh day, 7.4 mc. on the thirty-first day, and 13 mc. fifteen hours before death. Radiation surveys with a highly collimated counting system revealed significant localized deposition of gallium in the epiphyseal regions and more activity over bone than

over soft tissue in general. One area corresponding to the probably calcified tumor over the left diaphragm showed almost twice the activity of any other area.

About six blood samples were taken after each dose for radioassay. The gallium⁷² curve for disappearance from the blood stream followed an almost exponential form. Up to about 50 per cent of the initial level was obtained in twenty-four hours; to 20 per cent in forty-eight hours. After ninety-six hours the amount was below efficient counting levels.

All urine samples were assayed. Approximately 60 per cent of the total dose was excreted *via* the kidneys. Of this amount, two-thirds was excreted during the first eight hours following injection; nine-tenths the first day after injection. An insignificant proportion of the excreted gallium was found in the feces. Attempts were made to study excretion in sweat and saliva, but the samples were at background levels.

An interesting accumulation of gallium occurred in the pleural fluid. In Table XIX, the pleural fluid counting levels are compared with levels in the plasma withdrawn at about the same time. There was a significantly greater amount of gallium retained in the pleural fluid than in the plasma.

Autopsy Report: The body appeared extremely emaciated. There was very little subcutaneous fat. There were no abnormalities in the head, neck, abdomen, and extremities. The left leg had been removed by a disarticulation amputation.

The right pleural cavity was almost obliterated by extensive fibrous adhesions which were readily separated. The left pleural cavity contained a large quantity of turbid brown fluid with many masses of fibrin-like material. The right lung was fully expanded but was studded with numerous flat tumor nodules measuring up to 2 cm. in diameter. The left lung was collapsed except in the upper third. The periphery of this upper third was formed by a thick layer of hard yellow tumor with multiple areas

TABLE XX: RADIOASSAY OF AUTOPSY SAMPLES.
Patient G.P., 010003

	ACT/gm.*	DARH†	DARCB‡
MISCELLANEOUS ORGANS			
Thyroid	3,375	1.62	
Pituitary	3,545	1.66	
Right adrenal	3,431	1.65	
Left adrenal	4,882	2.35	
Right ovary	3,668	1.62	
Left ovary	3,955	1.90	
Breast	2,575	1.24	
Uterus	3,213	1.54	
Urinary bladder	8,888	4.28	
Kidneys	6.27×10^4	30.16	
Heart	2,079	1.00	
Brain	1,409	0.68	
Larynx	4,333	2.08	
Trachea	4,487	2.16	
Left lung	2.7×10^4	13.00	
Right lung	3.24×10^4	15.58	
Skeletal muscle	2,332	1.12	
Skin	3,474	1.67	
Spleen	4,599	2.21	
Cervical lymph node	5,977	2.91	
Mediastinal lymph node	5,600	2.69	
Small bowel mesentery plus nodes	3,901	1.88	
DIGESTIVE TRACT			
Tongue	3,859	1.86	
Salivary glands	3,092	1.49	
Esophagus	5,327	2.56	
Stomach	2,688	1.29	
Jejunum	1.08×10^4	5.19	
Ileum	8,072	3.88	
Cecum	5,212	2.51	
Transverse colon	4,672	2.25	
Rectum	3,119	1.50	
Liver	1.82×10^4	8.75	
Gallbladder	6,993	3.36	
Pancreas	5,372	2.58	
Bile	5,111	2.46	
BONE			
Sternum	2.21×10^4	10.64	2.42
Fifth left vertebra	4.68×10^4	22.52	5.14
Shaft of femur	9,113	4.38	1.00
Trochanter of femur	2.69×10^4	12.95	2.96
Calvarium	1.9×10^4	9.14	2.09
Mandible	3.0×10^4	14.44	3.30
Distal metaphysis of femur	2.99×10^4	14.38	3.28
Distal epiphysis of femur	3.38×10^4	16.26	3.71
Distal epiphysis line area, femur	6.5×10^4	31.29	7.14
Fatty marrow, femur	6,492	3.12	0.71
Tooth (1st molar)	9,719	4.68	1.07
Articular cartilage, distal femur	3,550	1.71	0.39
OSTEOGENIC METASTASES			
Left diaphragm	5.26×10^4	25.32	5.78
Thoracic aorta area	1.85×10^5	89.24	20.37
Thoracic aorta area	5.27×10^5	253.68	57.92
Right thorax, retropleural	1.84×10^5	88.56	20.22
Apex, left lung	2.7×10^4	13.00	2.97
Adjacent to left adrenal	1.24×10^4	5.96	1.36

Upper lobe, right lung	3.24×10^4	15.58	3.56
Bony nodule, right lung	1.64×10^5	78.88	18.00
Bony nodule, right lung	8.86×10^4	42.62	9.73
Bony nodule, right lung	1.41×10^5	67.82	15.48
Bony area, left lung	2.85×10^5	137.18	31.32
Left diaphragm	2.23×10^5	107.26	24.49

* ACT/gm. Counts per minute per gram tissue (c./m./g.) with standard corrections.

† DARH. Ratio of c./m./g. tissue to c./m./g. heart.

‡ DARCB. Ratio of c./m./g. tissue to c./m./g. cortical bone (shaft of femur).

of calcification. The lower two-thirds were completely collapsed and mostly replaced by firm tumor with patchy areas of calcification. The diaphragm on the left side was infiltrated with tumor. The heart appeared normal.

Microscopically the tumor was characterized by cells of the osteoblastic type interspersed with much osteoid tissue. There were patchy areas of calcification.

The final pathologic diagnosis was osteogenic sarcoma metastatic to the lungs, primary in the left femur.

In Table XX a detailed autopsy radioassay for this patient is presented. The distribution is remarkably like that shown in the rat. A few exceptions can be explained. The very high counts in the lung are an artifact, since no really normal lung was obtainable. Some tumor was present even in the very small pieces. The very high counts in the kidney samples can be explained on the basis of the time of death after the last dose. The patient died just after the height of the excretory phase. There is some indirect evidence of excretion through the liver into bile. The low count in the stomach, high in the jejunum, and decreasing down the intestine would suggest the possibility of reabsorption but probably indicates insufficient time for the activity to progress down the gastrointestinal tract. The patient was in a terminal state and normal peristaltic movement cannot be assumed.

The wide variations in the bone and tumor samples do not represent the degree of variation which may have actually existed. These samples were taken without reference to gross autoradiograms and may have missed the areas of lowest and highest deposition.

Table XVII lists the differential absorption ratios of various tissues as they are normalized to a heart value. This differential absorption ratio (H) value is the only valid comparative figure to use because of the variation in dosage, time of administration, and type of patient. The values were calcu-

lated from the average number of microcuries per gram of tissue as estimated from one to seven samples of similar tissues. The radiation values were corrected back to a "0" time, which was defined as the time of administration of the last dose of Ga^{72} received.

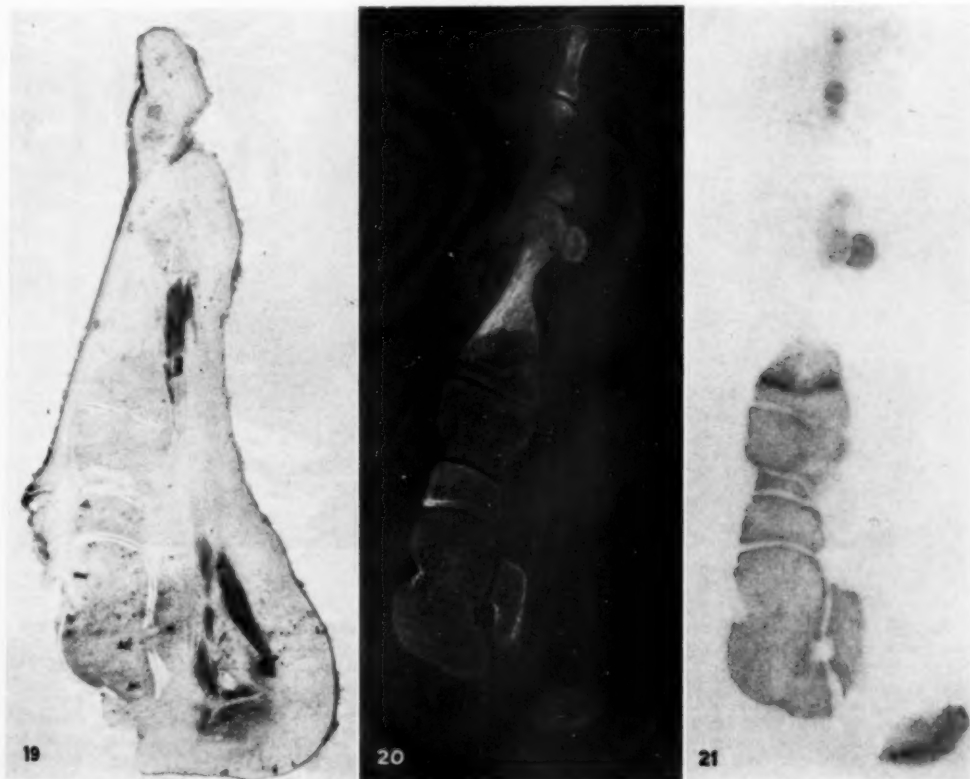
IX. Autoradiographic Studies

JOHN C. GALLIMORE, JR., M.S.,¹² GEORGE A. BOYD, M.S., GOULD A. ANDREWS, M.D.,
and MARSHALL BRUCER, M.D.

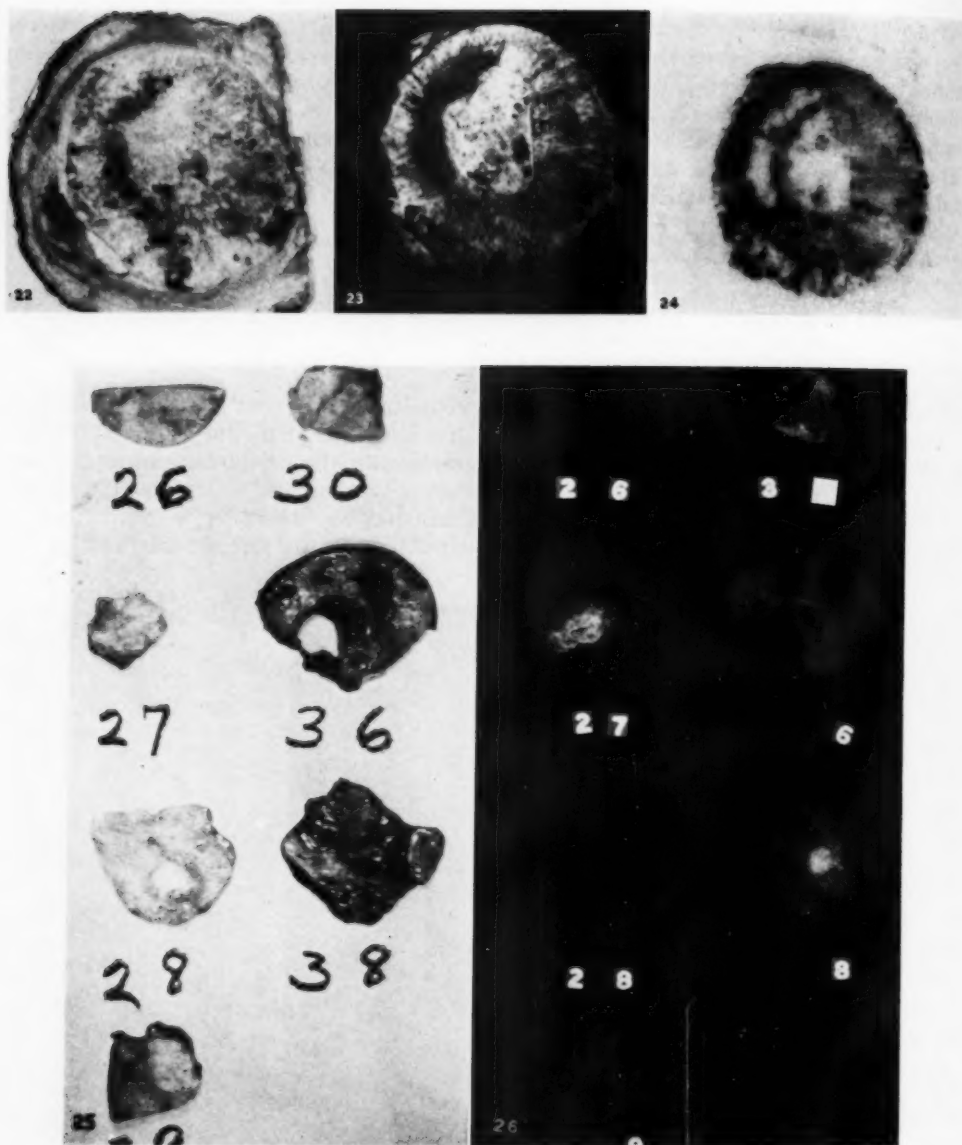
During the clinical studies on gallium⁷² a program of autoradiography was in the process of development. This was the first

group of patients on whom the Medical Division staff had prepared autoradiograms, and the methods were undergoing change during the course of the study. Consequently, there is a great deal of variability in the technic used and the re-

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Figs. 19-21. Patient H. D., No. 010016, 12-year-old female. Diagnosis: Osteogenic sarcoma, primary present. (Detailed history given in Section VI.) For detailed legends, see following page.



Patient H. D., No. 010016 (see also preceding page).

Fig. 19. Photograph of a gross specimen prepared after a high thigh amputation had been performed. The leg was frozen in dry ice and cut with a band saw. The specimen is a longitudinal section of the foot 2 mm. thick. No neoplasm or abnormality. The plicofilm which is used to separate the specimen from the film is apparent in the photograph.

Fig. 20. Roentgenogram of the specimen, showing the normal bone detail in a thin section of the foot.

Fig. 21. Autoradiogram prepared from the specimen shown in Fig. 20. The patient was given 22 mc. of Ga^{67} forty-eight hours before operation. The autoradiogram was exposed for twelve hours. It shows the normal distribution of gallium in bone. There is a prominent concentration at the epiphyseal line at the upper end of the metatarsal.

Fig. 22. Photograph showing a section through the thigh. This shows the osteogenic sarcoma involving the femur.

For legends of Figs. 23-26, see opposite page.

sults are not as suitable for a comparative analysis as they might otherwise have been.

Two methods for improving the usefulness of gross autoradiograms are apparent and are now being developed. One of these is the establishment of quantitative data so that, on the basis of the autoradiogram, it will be possible to determine the amount of the isotope in a given small volume of tissue. The other improvement is a better correlation of the histologic changes with the autoradiographic findings.

In spite of the limitations of these studies, they have contributed information not obtainable by other methods in the gallium study. They have shown in detail the distribution of gallium in some situations in which routine tissue assay methods are not sufficiently discriminating. They have served to emphasize the extremely uneven distribution of gallium in neoplastic metastases.

The autograms were prepared from specimens of tissue a few millimeters thick. Many of these were frozen in dry ice before cutting. They were cut by several methods. Most of the bone specimens were cut with a band saw. The exposure was made on Kodak x-ray, no-screen film; a sheet of plicofilm was used to separate the tissue from the film.

Figures 19-49 show photographs of gross

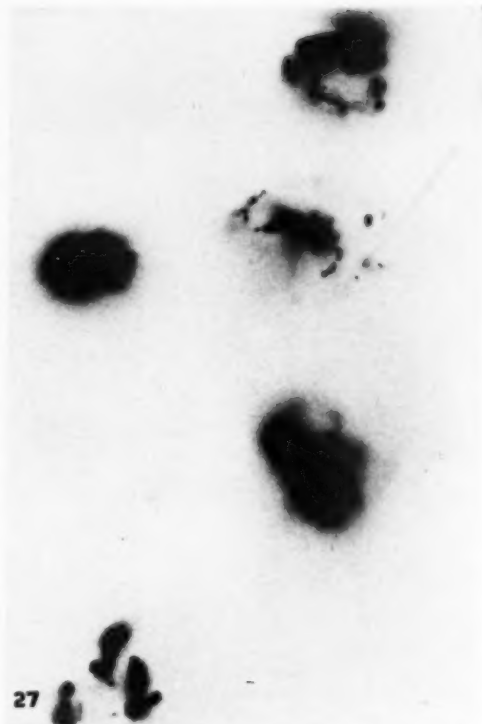


Fig. 27. Patient H. D., No. 010016. See also Figures 19-26. Autoradiogram prepared from the group of pulmonary metastases shown in Figs. 25 and 26. The patient had received 17.3 mc. of gallium⁶⁷ about two days before death. Comparison with the roentgenogram shows that the gallium distribution parallels calcification to a striking degree.

specimens, roentgenograms of these specimens, and the autoradiograms.

Patient H. D., No. 010016.

Fig. 23. Roentgenogram of the specimen shown in Fig. 22, showing the striking abnormal bone formation by the neoplasm.

Fig. 24. Autoradiogram, exposed for twelve hours, and therefore comparable quantitatively with the one of the foot from the same patient (Fig. 21). It is apparent that there is a heavy concentration of gallium in the neoplasm and that the concentration seems largely related to calcification in the tumor. Remnants of the normal cortex of the femur show very little gallium uptake, as is usual in normal bone. The usual periosteal and endosteal uptake is absent because of the presence of neoplasm.

This patient was subsequently treated with radioactive gallium and died several months later.

Fig. 25 shows a group of pulmonary metastases which had been separated from the lung parenchyma and arranged for section and autoradiogram.

Fig. 26 is a roentgenogram of these metastases. In many of them calcification is prominent.



Figs. 28-30. Patient D. A. (No. 010023), 17-year-old male. Diagnosis: Osteogenic sarcoma.

Fig. 28. Photograph of femur obtained at autopsy, after a course of gallium treatment. It does not contain any neoplasm. The patient had pulmonary metastases from a previously amputated primary lesion of the opposite femur. He had a striking pulmonary osteoarthropathy believed to be associated with the metastases.

Fig. 29. Roentgenogram of specimen in Fig. 28. Periosteal reaction with new bone formation is quite apparent.

Fig. 30. Autoradiogram from the same specimen. This patient had received 36.0 mc. of Ga^{67} approximately two days before death. The autoradiogram was exposed for twelve hours. There is a striking concentration of gallium associated with the periosteal proliferation.



Figs. 31-33. For legends, see top opposite page.

Figs. 31-34. Patient M. L. H. (No. 010041), 37-year-old male. Diagnosis: Malignant plasmocytoma. Death after a dose of gallium had been given for excretion and biopsy studies.

Fig. 31. Photograph showing the upper end of a femur and the head of the femur which were broken during autopsy in spite of care in manipulation. It is apparent that the upper end of the femur is extensively involved by the plasmocytoma.

Fig. 32. Roentgenogram of specimen shown in Fig. 31. Extensive bone destruction due to malignant plasmocytoma is apparent.

Fig. 33. Autoradiogram from same specimen. The patient had received 23 mc. of Ga^{72} approximately two and a half days before death. The exposure was for twenty hours. There is a very distinct concentration of the gallium related to the lesion. It appears that the concentration is greatest at the edge of the tumor, where there is contact with residual normal bone.

Fig. 34. Roentgenogram of skull, revealing destructive lesions.

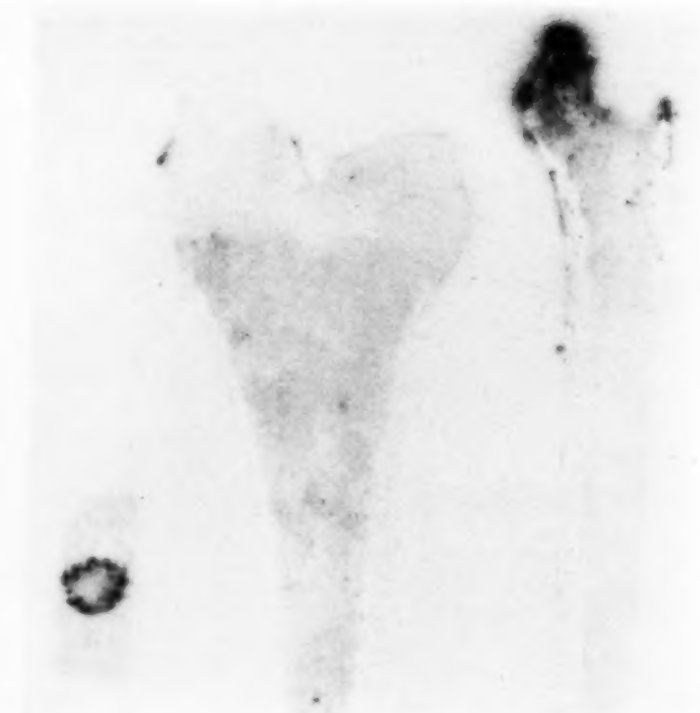


Fig. 35. Autoradiograms from the patient shown in Figs. 31-34. This is reproduced chiefly for the skull lesion, which appears in the form of a rectangular specimen at the left. This was a characteristic "punched out" lesion of malignant plasmocytoma in the skull. A section of bone was cut so as to include the lesion. The center consisted of well preserved malignant plasmocytic cells. It is apparent that the gallium concentrated at the periphery of the lesion, where normal bone was involved. This specimen was also exposed for twenty hours.

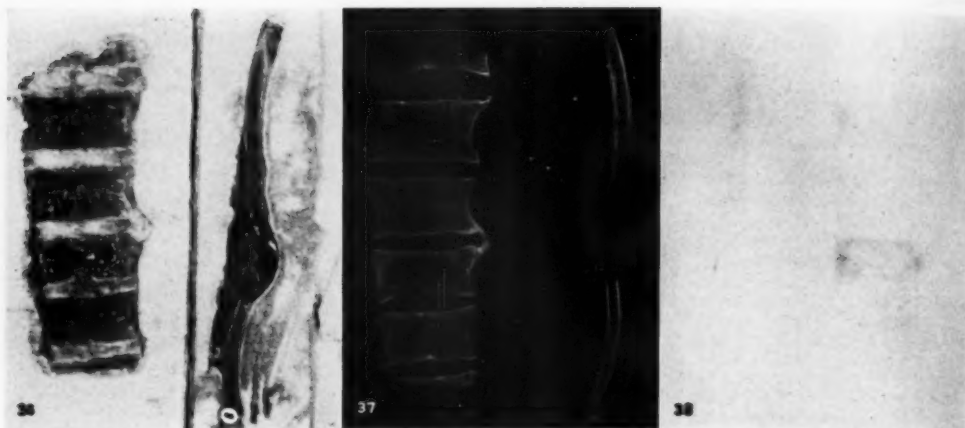


Fig. 36-38. Patient J. F. (No. 010049), 51-year-old male. Diagnosis: Adenocarcinoma of right kidney with metastases to bone. This patient had destructive bone metastases and died during a course of gallium treatment.

Fig. 36. Photograph of gross specimens imbedded in plaster for autoradiography. It shows a rib with an extensive destructive lesion and a section of spine, with a vertebral body invaded by neoplasm.

Fig. 37. Roentgenogram of specimens shown in Fig. 36. The left specimen has been inverted so that it is a mirror image of the one shown on the preceding photograph. The bone destruction caused by neoplasm and some hypertrophic lipping of the vertebral bodies are shown.

Fig. 38. Autoradiogram prepared from the same specimens. The patient had received 15.8 mc. of gallium about three days before death. The autograms were exposed for four days. The section of vertebral bodies is on the left and the section of rib on the right. The section of rib is in the same position as on the photograph and is opposite to its position shown in the roentgenogram. The rib shows only a few scattered spots of radioactivity. The vertebral body shows a distinct concentration of the gallium in the area involved by neoplasm.



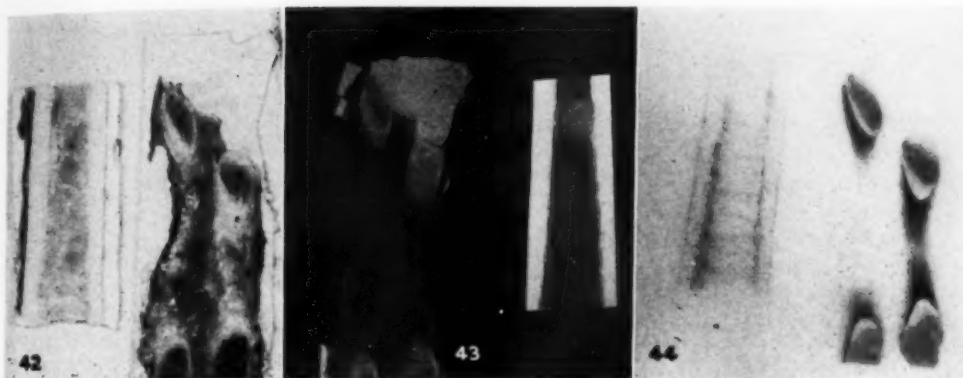
Figs. 39 and 40. Photograph and autoradiogram of kidney of patient shown in Figs. 36-38.

Fig. 39. Kidney containing primary lesion. The more uniform appearing tissue is residual normal kidney.

Fig. 40. The small amount of gallium present is almost exclusively in the normal kidney and is absent in the neoplasm.



Fig. 41. Patient B. D. (No. 110061), 16-year-old male. Diagnosis: Osteogenic sarcoma. This patient received 21 mc. of gallium approximately two days before death. The above autogram is made from a section of normal kidney. It was exposed for three hours.

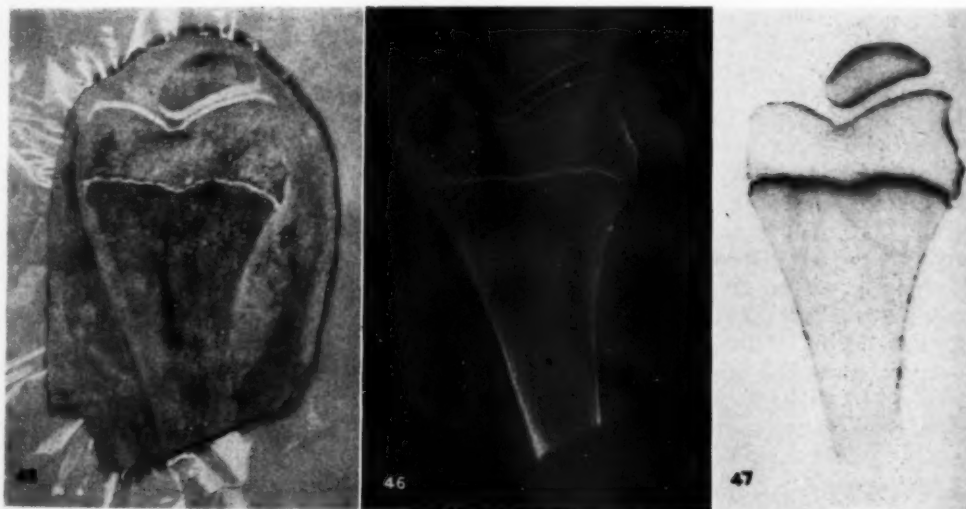


Figs. 42-44. Patient B. D. (No. 110061), with osteogenic sarcoma.

Fig. 42. Photograph showing gross specimen of ribs and shaft of femur mounted in plaster for autogram preparation.

Fig. 43. Roentgenograms of specimen showing bone detail.

Fig. 44. Gross autogram. Exposure was for three hours. There is a striking concentration of gallium in the periosteum of the ribs. The femur shows a delicate pattern of gallium along the endosteum, periosteum, and trabecular structures.

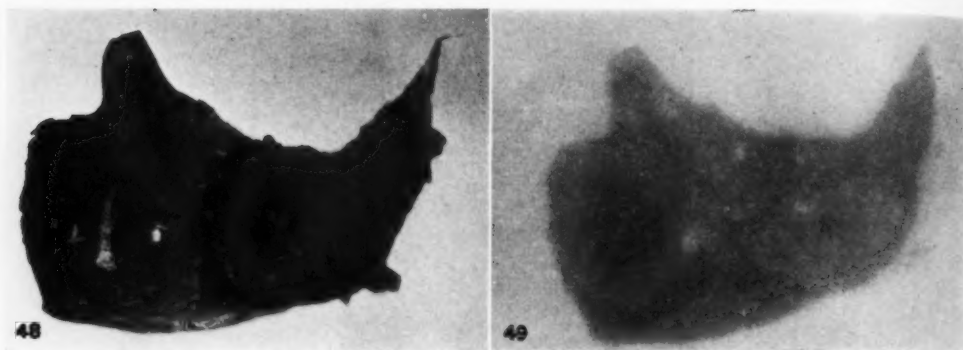


Figs. 45-47. Patient F. T. (No. 110073), 13-year-old male. Diagnosis: Osteogenic sarcoma; lung metastases; primary present.

Fig. 45. Photograph of the gross specimen obtained at amputation. The pliofilm covering is visible. Many other autograms were prepared from this patient but the one presented here is shown to indicate normal bone detail.

Fig. 46. Roentgenogram of the specimen shown in Fig. 45.

Fig. 47. Autoradiogram from specimen shown in Figs. 45 and 46. The patient had been given 20.4 mc. of gallium forty-eight hours before amputation. The exposure was for six hours. This shows the concentration of gallium at the epiphysis in a young patient.



Figs. 48 and 49. Patient A. A. (No. 110117), 56-year-old female. Diagnosis: Malignant plasmocytoma.

Fig. 48. Gross photograph showing section of liver prepared for autoradiography.

Fig. 49. Autoradiogram prepared from the liver slice shown in Fig. 48. The patient had received 5.7 mc. of gallium five and a half hours before death. Exposure was approximately nineteen hours. There is a rather uniform distribution of gallium in the liver.

X. Preliminary Data on Gallium⁶⁷

H. D. BRUNER, M.D., RAYMOND L. HAYES, PH.D., and JESSE D. PERKINSON, JR., PH.D.

These studies on Ga⁶⁷ were carried out in the belief that the metal's bone-seeking properties had not been fully exploited by the low specific activity Ga⁷² available from the Oak Ridge reactor. The short half-life of Ga⁷², 14.3 hours, became a further disadvantage when it developed that the biochemical processes giving the desired differential localization were slower than the physical decay. Thus, much of the radiation was expended before the isotope had been differentially localized. Finally, the metal poisoning from the unavoidably present stable gallium limited the amount of radioactive Ga⁷² which could be administered.

All these very important practical objections apparently could be circumvented by use of Ga⁶⁷, provided it behaved like Ga⁷² in the body. The following basic experiments were designed to check this point, using for comparison the data reported in Section V of this series.

1. PHYSICAL DATA

Ga⁶⁷ is prepared by a ($p, 2n$) reaction with very high purity zinc in a 25-mev cyclotron. Except for Ga⁶⁷, all of the gal-

lium radioisotopes also formed are relatively short-lived, so that after ninety-six hours, with a loss of slightly more than half the original Ga⁶⁷ content, the target drops to a radiation level reasonably safe for processing. The extraction of gallium by isopropyl ether from 7 *N* HCl is remarkably complete and yields a carrier-free preparation (26). The term "carrier-free" is used in the sense that the concentration of the stable gallium isotopes, Ga⁶⁹ and Ga⁷¹, was below the limit of spectrographic detectability, which was 2×10^{-7} gm. of gallium per milliliter on the instrument available. Actually, there must have been present some stable gallium which originated from impurities in the target and from subsidiary nuclear reactions giving chiefly Ga⁶⁹. Since 1 mc. of Ga⁶⁷ weighs 1.67×10^{-9} gm., the total gallium content of the solutions was between 2×10^{-7} and 2×10^{-8} gm. per milliliter.

The partial decay schemes of Ga⁶⁷ stated in source books (27) were inadequate for calculating the probable tissue radiation dose. This necessary datum was provided by Doctors A. R. Brosi and B. H. Ketelle of the Chemistry Division of the Oak Ridge

National Laboratory, who carried out original studies upon our request. They have suggested the decay scheme shown in Figure 50, using portions of three of the four runs of Ga⁶⁷ prepared for the animal experiments reported below. The scheme and values are provisional and subject to modification on publication of the complete data, but such revision will be minor and will not significantly change the values in this report. It will be noted that there is one 8.6 kev *K* capture x-ray per disintegration, followed by a gamma ray, or, in some cases, a cascade of gamma rays. The weakest gamma ray, 94 kev, was found to undergo internal conversion in 40 per cent of cases. For dosage purposes, this is the equivalent *per disintegration* of one electron with a range of approximately 5 mm. plus 0.264 essentially monochromatic internal conversion electrons having a range of 0.13 mm. Thus, some of the energy of disintegration is expressed as electrons of high specific ionization and very short range.

The remaining gamma rays are therapeutically undesirable in that they give rise to a cross-fire effect on distant tissues which amounts to whole-body irradiation. Nevertheless, the inverse-square law favors the deposition of energy in the immediate vicinity of a local concentration of such a gamma-ray-emitting isotope.

The half-lives of these four samples of Ga⁶⁷ as determined by a liquid counting system and a bismuth-wall gamma-counter tube was 3.24 days and ranged between 3.17 and 3.28 days (76.1 to 78.7 hours) by least-squares computation. This contrasts with values of 83 hours observed by Dudley (18) in samples of Ga⁶⁷ produced by (*d*, *n*) and extracted differently. The half-lives obtained by Brosi and Ketelle with their refined instruments correspond to the seventy-eight-hour half-life. In this report, the 3.24-day half-life and 4.67-day (112.1 hours) mean-life will be used.

Using the formulations of Marinelli, Quimby, and Hine (3) and the above decay data, the radiation doses given in Table XXI were calculated on the basis of the

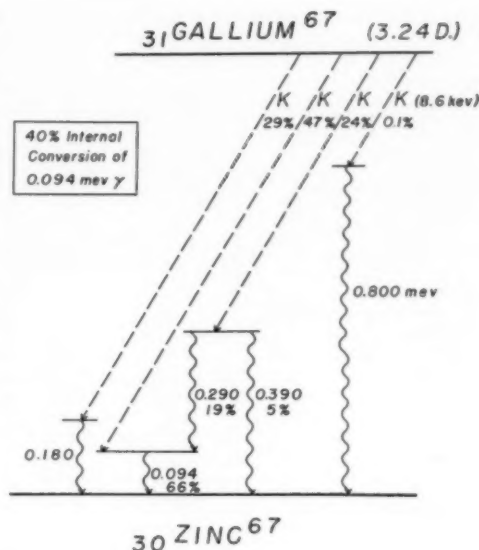


Fig. 50. A simplified decay scheme of Ga⁶⁷ with a half-life of 3.24 days.

TABLE XXI: RADIATION DOSAGE COMPUTED FOR 1 MICROCURIE OF Ga⁶⁷ OR Ga⁷³ COMPLETELY DECAYING IN 1 GRAM OF TISSUE LOCATED AT THE CENTER OF THE THEORETICAL CYLINDER OF THE BODY (4)

		Total Roentgens	Beta Component	Gamma Component
Ga ⁶⁷ (T _{1/2} = 3.24 days)	Man	28.97	9.53	19.44
	Rat	14.47	9.53	4.94
Ga ⁷³ (T _{1/2} = 14.3 hr.)	Man	79.00	20.60	58.40
	Rat	35.05	20.60	14.45

roentgens or rep arising from the complete disintegration of 1 mc. in 1 gm. of tissue. The analogous data for Ga⁷³ are added for comparison.

The I gamma value weighted for the frequency and energy of the various gamma-ray components was computed as 0.975 r/mc.-hr. at 1 cm.; this is 11 per cent of the 8.4 r/mc.-hr. for radium.

2. DISTRIBUTION OF CARRIER-FREE GA⁶⁷ IN THE RAT

Procedure: Thirty-two male white rats weighing 240 ± 30 gm. received carrier-free Ga⁶⁷ by the intravenous route. This solution contained 0.15 mg. of citric acid per milliliter to insure complexing and was adjusted to pH 7.4. The original Ga⁶⁷ solu-

TABLE XXII: DISTRIBUTION OF Ga^{67} IN SELECTED ORGANS OF RATS AT VARIOUS TIMES AFTER INTRAVENOUS ADMINISTRATION OF THE CARRIER-FREE Ga^{67} CITRATE COMPLEX

Day sacrificed Number of rats	1 6	3 6	5 6	10 5	15 5	20 4
Estimated cumulative dose in roentgens	0.22-1.08	0.80-2.14	1.85-8.10	11.12-18.25	55.20-144.0	165.0-284.0
A. Per cent retained	78.6	65.6	60.7	52.5	48.3	45.1
Per cent excreted	21.4	34.4	39.3	47.5	51.7	54.9
Fraction in:						
Urine	0.70	0.55	0.52	0.49	0.49	0.48
Feces	0.30	0.45	0.48	0.51	0.51	0.52
B. Total organ content in per cent of original dose						
Blood plasma	1.56	0.55	0.21	0.10	0.08	0.15
Blood cells	0.15	0.18	0.08	*	*	*
Liver	21.39	13.97	12.40	4.28	2.76	2.87
Spleen	1.27	1.17	1.19	0.99	0.87	1.23
Kidney	0.89	0.89	0.77	0.66	0.56	0.63
Heart	0.07	0.07	0.07	0.06	0.05	0.05
Femur	1.21	1.12	1.01	0.72	0.91	1.05
Skeleton†	26.25	26.07	25.32	16.19	21.79	23.43
Remainder	25.15	21.65	19.67	29.45	21.25	15.69

* Negligible.

† Calculated as 7.06 per cent of the body weight times the activity per gram of femur.

tions were diluted with blank citrate of the same concentrations and pH, since the rats sacrificed on the first day required only 1/130 as much Ga^{67} as those sacrificed on the twentieth day. Thus, all animals received identical injections except for the content of Ga^{67} , for an excess of radioactivity was experimentally undesirable. The largest amount of gallium was below spectrographic detectability.

The rats were housed in individual cages which permitted collection of urine and feces without contamination of each other (24). At one, three, five, ten, fifteen, or twenty days after injection, the rats were nembutalized, viviperfused with 200 ml. of saline, and the tissue was analyzed for Ga^{67} after being digested with HNO_3 . A bismuth-wall Geiger-Müller tube mounted vertically in a lead shield counted the gamma rays according to the method described by Marinelli (28). The samples were counted to obtain a standard deviation of 2 per cent or less, or 5 per cent or less when the net count was very low, *i.e.*, less than twice background. In other respects, the experimental procedures were as described in Sections III and V of this series, except that the prophylactic dose of calcium was omitted.

Results: At the top of Table XXII are shown the numbers of animals and the estimated minimum and maximum whole-body radiation doses accumulated at time of sacrifice. Below, in order, are: (A) The average cumulative percentage of the total dose which was excreted or retained and the partition of the excreted fraction between urine and feces; (B) the average percentage of the injected dose retained by the organs or tissues listed. No great error was introduced by neglecting the weight of the organs, since the animals were of essentially the same size and the dose was calculated relative to weight. Each value in the table is the average for the number of animals indicated at the top of the table. The standard deviations, corrected for the small samples, ranged between 10 and 30 per cent of their respective means in most cases, but the liver and blood-cell fractions in some instances had standard deviations as much as 50 per cent of their means. In contrast, those for the femur were regularly about 10 per cent, except for the ten-day animals, 2 of which unaccountably gave distinctly lower values to break an otherwise smooth trend. On the whole, however, these means represented the central tendency reasonably well.

The data in Table XXII show that the liver lost most of its initial Ga⁶⁷ content, while the bone and sixteen other organs (some not shown in the table) retained most of their initial uptake during the twenty-day period. The continued presence of small amounts of Ga⁶⁷ in the plasma suggests that plasma was acting as a transport-equilibration agent, as it does for iron.

The tissue distribution of the isotope retained at each interval is expressed in Table XXIII in terms of Marinelli's differential absorption ratio (3), which is computed as:

$$\frac{\text{Activity per gram of tissue}}{\text{Total retained activity} + \text{body weight}}$$

This ratio permits inter-comparison of the relative Ga⁶⁷ concentrations in the various tissues of the different groups of animals by normalizing initial dose, body weight, excretion, and variations of organ weights. During the first half-life of Ga⁶⁷, the first three days after injection, the liver, spleen, and femur showed approximately equal retention at a level about three times higher than the next tissue, the kidney. After the third day, the spleen had the highest relative concentration, not because it picked up additional amounts, but because it lost relatively less than the other

TABLE XXIII: AVERAGES OF THE DIFFERENTIAL ABSORPTION RATIOS OF TISSUES OF RATS SACRIFICED AT THE INDICATED TIMES AFTER INTRAVENOUS ADMINISTRATION OF CARRIER-FREE GA⁶⁷ CITRATE COMPLEX

Day of sacrifice	1	3	5	10	15	20
Number of rats	6	6	6	5	5	4
Liver	7.1	5.8	5.5	2.4	1.7	1.8
Spleen	5.1	6.9	8.1	8.5	8.0	10.3
Kidney	1.3	1.7	1.5	1.5	1.3	1.8
Heart	0.3	0.3	0.3	0.3	0.3	0.4
Lung	0.9	0.7	0.8	2.1	0.8	1.7
Lymph nodes	1.4	1.6	1.8	1.8	2.9	1.4
Blood plasma	0.7	0.2	0.1	0.1	0.1	0.1
Blood cells	0.1	0.1	0.1	*	*	*
Skeletal muscle	0.3	0.2	0.2	0.5	0.5	1.0
Skin	0.4	0.3	0.3	0.3	0.3	0.4
Teeth	2.8	4.4	4.9	6.5	6.3	8.2
Mandible	4.0	5.0	4.8	4.7	6.5	7.4
Calvarium	2.3	2.8	3.1	2.6	4.1	4.2
Femur	4.7	5.6	5.9	4.4	6.5	7.4
Shaft	5.0	6.1	6.2	4.4	7.3	7.7
Epiphyses	4.3	4.9	5.4	4.5	5.6	7.1

* See footnote to Table XXII.

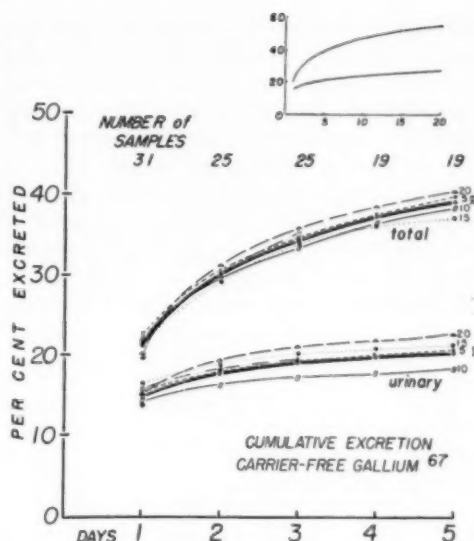


Fig. 51. The total and urinary excretion of Ga⁶⁷ during the first five days after injection of the carrier-free Ga⁶⁷ stabilized at pH 7.4 with citrate. The average values for all groups are shown by the heavy lines. The light lines represent the averages of each group separated according to time of sacrifice, which was associated with size of dose and total radiation received (Table XXII). The mean excretion values for the entire twenty days are shown in the upper right-hand box.

tissues, as can be seen from Table XXII. The liver differential absorption ratio decreased sharply between the fifth and fifteenth day and thereafter held a low level about equal to the kidney, lung, and lymph nodes. The femur showed a mild increase after the first day, the figure remaining at about 0.75 the spleen value. Of the several types of osseous tissue analyzed, the incisor teeth, including the pulpy roots, gave the highest values, followed closely by the shaft of the femur. Sixteen additional tissues (most are omitted from the table) showed differential absorption ratios of 1.0 or less, although for some tissues a distinct trend could be made out, as for the lymph nodes in Table XXIII.

The urinary excretion during the first twenty-four hours following injection was 2.5 times that in the feces, but thereafter the feces contained 1.5 to 3.0 times as much activity as the urine per daily collection period (Fig. 51). Forty per cent of

the total dose was excreted by the fifth day and 57 per cent (range 51.9 to 67.3 per cent) by the twentieth day. The average 50 per cent excretion point, the biological half-life (3), occurred on the thirteenth day. The separate average excretion patterns for the various groups of rats (Fig. 51) were essentially identical, despite the range of radiation and metal dosage. Although the level of metal dosage is so small that a hundredfold variation is not detectable,

differential absorption ratio of the femur was about four times greater than that of the liver, the next most active tissue at twenty-four hours (3.3 hours beyond the mean-life of Ga^{72}). At ninety-six hours, the femur was twelve to fourteen times more active than the spleen; during that time the liver had lost much of its gallium, while the femur and spleen had not. The cumulative excretion over ninety-six hours totaled 76 per cent, with the urine contributing 8.5

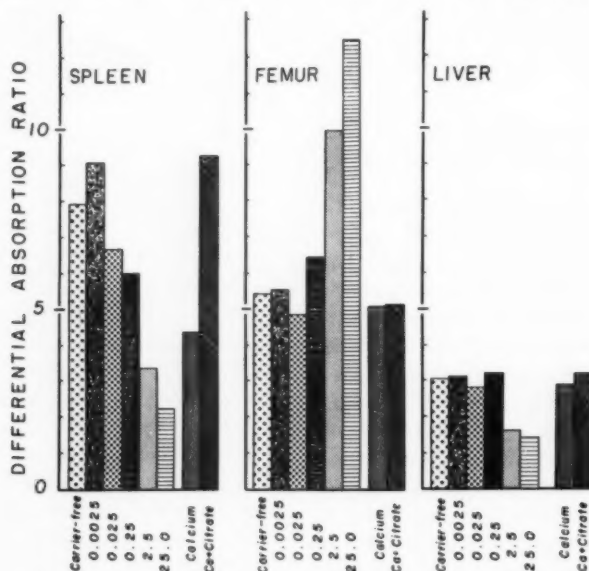


Fig. 52. Histogram of the data of Table XXV, showing the relation of the differential absorption ratio to dose level of carrier gallium in milligrams per kilogram. The metal was injected intravenously five days previously as the citrate complex. The two control groups received calcium plus tracer Ga^{72} , and calcium plus tracer Ga^{72} plus Na citrate in the amounts used at the 25 mg./kg. dose level.

such a range in radiation dosage might well have affected body water-excretion processes. For example, the twenty-day rats received about 100 times as much radiation over the first twenty-four hours as the rats which were sacrificed at twenty-four hours, but the excretion patterns of the two were similar.

Discussion: These results differed significantly from those in Section V, which dealt with the distribution of Ga^{72} -labeled gallium citrate administered at the mg./kg. dose level. In those experiments, the dif-

ferences were as much as the feces. Also, at this mg./kg. level of carrier gallium, a fifty-fold variation in dose of metal produced significant differences in the total amount excreted during the first twenty-four hours and in the urine/feces ratio. The above carrier-free results, therefore, differed in: (a) percentage of the dose excreted, (b) the pattern of excretion, (c) the absence of changes in excretion pattern when the concentration of metal was varied more than a hundredfold, and (d) the time changes and inter-relations of the differ-

TABLE XXIV: DISTRIBUTION OF GALLIUM IN THE ORGANS OF RATS SACRIFICED FIVE DAYS AFTER INTRAVENOUS ADMINISTRATION OF INCREASING DOSES OF CARRIER GALLIUM CITRATE COMPLEX TRACED BY Ga⁶⁷

Dose in mg. Ga/kg.	0.00	0.0025	0.025	0.25	2.5	25.0	Ca Control	Ca + Cit Control
Number of rats	4	4	4	4	4	4	4	4
A. Per cent retained	56.1	59.2	59.7	47.9	31.1	18.5	62.0	57.4
Per cent excreted	43.9	40.8	40.3	52.1	68.9	81.5	38.0	42.6
Fraction in:								
Urine	0.51	0.49	0.52	0.67	0.81	0.91	0.53	0.55
Feces	0.49	0.51	0.48	0.33	0.19	0.09	0.47	0.45
B. Total organ content in per cent of original dose								
Blood plasma	0.16	0.24	0.18	0.25	0.15	0.07	0.23	0.22
Blood cells	0.07	0.07	0.05	0.06	*	*	0.07	0.03
Liver	5.81	6.52	6.37	5.88	1.83	0.98	6.64	6.09
Spleen	1.66	1.46	0.85	1.00	0.31	0.13	1.10	1.86
Kidney	0.92	0.95	0.81	0.85	0.38	0.19	1.10	0.83
Heart	0.06	0.07	0.06	0.05	*	*	0.07	0.06
Skeleton†	21.57	23.19	23.63	21.58	21.65	15.72	22.14	20.07
Remainder	25.88	26.73	27.71	18.19	6.78	1.41	30.66	28.23

* and † See footnotes to Table XXII.

tial absorption ratios of femur, liver, spleen, and other organs to one another.

Because of the following additional variables, it cannot be assumed that the presence or absence of carrier gallium was solely responsible for these differences: (1) Ga⁶⁷ was used for the carrier-free experiment, whereas Ga⁷² acted as the "tracer" for the stable Ga^{69, 71}, which was unavoidably mixed with Ga⁷². The conventional assumption is that body mechanisms cannot distinguish between the isotopes of elements above carbon but, in the absence of data to the contrary, it should be regarded solely as an assumption. (2) The associated radiation doses differed both as to total amount, timing, and, in consequence of the different differential absorptions, the distribution over the body. (3) In the carrier-free experiments, the total amount of citrate injected was approximately 10 µg. and was not preceded by calcium.

The following experiment, therefore, was planned in order to minimize or control these variables while bringing together the preceding experiments which had dealt with the extremes of carrier dosage.

3. EFFECT OF THE QUANTITY OF GALLIUM ON ITS DISTRIBUTION

The essential design of this experiment was to use carrier-free Ga⁶⁷ to "trace"

stable Ga^{69, 71}, which was varied by a factor of 10 over 5 orders of magnitude, holding constant the mol ratio of gallium to citrate to calcium ions and the total volume of injections.

Procedure: Thirty-two male white rats weighing 250 ± 20 gm. were divided at random into eight groups of 4 animals each. For each rat a constant amount of carrier-free Ga⁶⁷ was taken, to which was added carrier Ga^{69, 71} citrate in proportion to body weight plus saline to make 1 ml. The quantity of carrier was adjusted to give dose levels of 0.00 and 0.0025, 0.025, 0.25, 2.5 and 25.0 mg. of gallium per kilogram of body weight for six of the eight groups. These mixtures, preceded by the requisite amount of calcium gluconate, were injected intravenously *via* the tail vein, as described in detail in Section IV. The mol ratios of gallium to citrate to prophylactic calcium ion were maintained in all groups at 1.0 to 1.2 to 2.4. Sterile physiological saline was used to dilute the concentrated solutions appropriately and to wash in the injections.

The two remaining groups served as controls against the possible effects of the calcium or the calcium-plus-citrate injections. One group of 4 rats received calcium gluconate followed by carrier-free Ga⁶⁷ and saline in the amounts used at the 25 mg./

TABLE XXV: AVERAGES OF THE DIFFERENTIAL ABSORPTION RATIOS OF TISSUES OF WHITE RATS SACRIFICED FIVE DAYS AFTER INTRAVENOUS ADMINISTRATION OF INCREASING AMOUNTS OF CARRIER GALLIUM CITRATE TRACED BY Ga^{67}

Dose in mg. Ga/kg.	0.00	0.0025	0.025	0.25	2.5	25.0	Ca Control	Ca + Cit Control
Plasma	0.08	0.12	0.09	0.14	0.13	0.09	0.20	0.10
Blood cells	0.03	0.03	0.02	0.04	0.02	0.02	0.04	0.02
Liver	3.06	3.08	2.76	3.21	1.61	1.40	2.83	3.17
Spleen	7.91	9.03	6.66	6.01	3.29	2.17	4.29	9.21
Kidney	2.10	1.94	1.60	1.94	1.51	1.33	1.98	1.67
Heart	0.30	0.33	0.28	0.27	0.15	0.11	0.31	0.27
Femur	5.45	5.55	5.34	6.39	9.89	12.42	5.06	5.13
Remainder	0.88	0.86	0.85	0.86	0.92	0.91	0.85	0.87

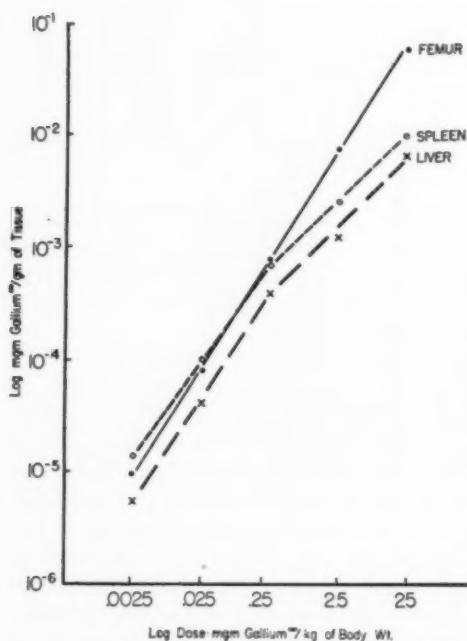


Fig. 53. The log of the absolute milligrams of gallium retained per gram of spleen, femur, and liver was plotted against the log of the dose in mg./kg. of body weight.

kg. dose level of carrier gallium. The other received calcium gluconate followed by carrier-free Ga^{67} plus sodium citrate adjusted to pH 7.4 and saline in amounts used for the 25 mg./kg. dose level. All animals were sacrificed one hundred and twenty hours after injection. They were viviparous, and the activities of the tissues were determined as described above (p. 604). These experiments were comparable to the others of the series in all other respects.

Results: The distribution and excretion

patterns of gallium in the carrier-free and low-dose groups (Tables XXIV and XXV) matched the analogous data for rats killed at five days in the preceding experiment (Tables XXII and XXIII). On the other hand, the results for the 2.5 and 25 mg./kg. groups agreed with the four-day data of the Ga^{72} tracer experiments described in Section V. Thus, the metabolic processes of the rat apparently were not able to distinguish between Ga^{67} and Ga^{72} and, hence, between Ga^{69} and Ga^{71} , the stable isotopes. An isotope effect did not appear in these experiments.

The distribution of gallium seems not to have been affected by differences in the radiation emitted by these two isotopes. The differences were both in the absolute radiation dose, as shown in Table XXI, and in the rate of delivery of the dose to tissues due to the differences in half-life and shifts about the body relative to time. Thus, the five-day cumulative whole-body dose for the Ga^{67} rats was estimated to be about 5 r received more or less exponentially over the five days, whereas, the 25 mg./kg. Ga^{72} rats received about 80 r exponentially over the first day.

With one exception, the data of the two control groups coincided closely with the corresponding carrier-free and low-carrier-dose groups (Tables XXIV and XXV and Fig. 52). The exception, the spleen of the calcium control, was the result of one anomalous low value. Otherwise, the data indicate that the calcium alone, or the calcium plus citrate, did not significantly influence the distribution of the element. On the other hand, because calcium and

citrate are present in blood and tissues, a really good experimental control cannot be obtained until another salt satisfactory for intravenous injection is found. Thus, it cannot be absolutely denied that calcium or calcium plus citrate was necessary for the observed changes. Nevertheless, the abrupt shift within a continuous series which was designed on constant mol proportion procedures, identified gallium as the important variable.

Figure 52, prepared from the data of Table XXV, shows that a change in the relative distribution of Ga⁶⁷ occurred when the amount of carrier Ga^{60,71} exceeded the 0.25 mg./kg. level. Above this dose, the five-day differential absorption ratio of the femur sharply increased. At the same time that of the spleen and liver, and to a lesser extent that of the lung, heart, and lymph nodes, decreased significantly. Thus, the relative concentration of gallium was higher in the spleen than in the femur at low carrier doses, but this relation was inverted at the high levels. The point of inversion was between 0.25 and 2.5 mg. of gallium per kilogram.

Figure 53 and Table XXIV indicate that this differential in favor of the femur was not due to the bone retaining a relatively larger fraction of the higher doses of gallium; instead, the other organs retained less. By plotting the log of the absolute milligrams of gallium retained per gram of a tissue against the log of the dose in milligrams per kilogram of body weight, linear relationships were obtained. These retention curves for the spleen and liver were inflected at the 0.25 mg./kg. dose and, in so far as three points warrant, the slopes were essentially linear both below and above the point of inflection. The retention by the femur, on the other hand, was essentially linear over five orders of magnitude on both axes; however, the somewhat lower value for the femur at the 25 mg./kg. dose suggests that this tissue, too, was beginning to shade off. Such linear relationships correspond to the formula $Y = a \cdot X^b$, but in view of the small numbers of animals no attempt was made

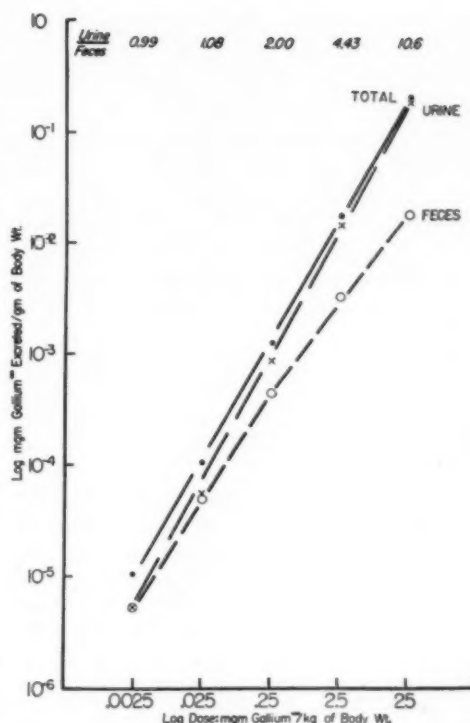


Fig. 54. The log of the absolute milligrams of gallium per kilogram excreted in the urine or feces, and the total excretion, was plotted against the log of the dose of gallium in milligrams per kilogram of body weight. The urine to feces ratio at the various dose levels is given across the top.

to obtain the numerical values of the constants a and b .

The excretory pattern altered as the dose of carrier gallium increased. As shown in Table XXIV and at the top of Figure 54, the urine and feces contributed about equally to the five-day total excretion at doses of carrier between 0.00 and 0.25 mg./kg. Above this level the urine/-feces ratio increased, finally reaching 10.5 at the 25 mg./kg. dose. In all instances, the bulk of the urinary excretion occurred during the first twenty-four hours after injection; thereafter, the feces carried as much or more gallium than the urine per twenty-four-hour collection period. Figure 54, which is a log-log plot of the absolute amount of gallium in the urine and feces relative to dose of carrier, makes it clear

that this seeming predominance of the urinary route was the result of decreased fecal excretion. Urinary excretion proceeded linearly over this 10^5 dosage range, while the fecal excretion showed a point of inflection at the 0.25 mg./kg. of carrier level of the liver and spleen in Figure 53. The data in Table XXV and Figure 54 make clear the sequences in the transition from the carrier-free pattern in section 2 above to that seen in the large carrier dose experiments using Ga^{72} in Section V.

Discussion: These data show that the quantity of gallium administered influenced the manner in which the metal was distributed and excreted by the rat. So far as is known, this point has not been studied in detail with reference to a substance essentially foreign to animal metabolic processes. A carrier effect on iodine uptake by the thyroid is now well recognized and more recently a carrier effect has been described for Ca^{45} (29), but in both instances the isotopes were added to an already existing metabolic pool of the element. The added labeled atoms were, therefore, competing with the rest of the pool for the metabolic processes responsible for the uptake. How successful they were would depend upon the relative number of labeled and stable atoms in the pool. In the case of calcium, the number of atoms in the blood pool is very large, 5.4×10^{21} compared to the 7×10^{14} in a millicurie of carrier-free Ca^{45} . The absolute size of the iodine pool (1.2×10^{18}) is much smaller than that of the calcium, but still very large compared with the 3.7×10^{13} I^{131} atoms in a 1-mc. carrier-free dose. The addition of carrier has the effect of enlarging the pool, diluting the radioisotope, and decreasing the chance that a given radioactive atom will be metabolized in a particular way and time.

Gallium presents a different problem in that it is normally absent from body tissues except for traces in bone (11), *i.e.*, less than 1 $\mu\text{g.}$ per gram or 1 part per million, the limit of chemical analysis. However, because gallium occurs in all materials containing aluminum and zinc, it would be expected

that some gallium must be present in blood. The 25, 2.5, and 0.25 mg./kg. doses of carrier would produce initial average concentrations of 25, 2.5, and 0.25 $\mu\text{g./gm.}$ respectively. Such concentrations are well above the concentrations which might normally exist in blood, but the still lower doses would give concentrations in the same range as blood. A ratio of injected gallium to normal blood content of possibly 10^{-1} to 10^2 is, however, quite different from the ratios for Ca^{45} and I^{131} , which would be in the range of 10^{-5} to 10^{-7} . Thus, except at the carrier-free dose, it is difficult to think that the injected gallium competes for the biological processes in the sense that I^{131} or Ca^{45} does.

The data in Figures 53 and 54 suggest a different possibility. Such linear relationships on log-log paper, corresponding to $Y = a \cdot X^b$, occur regularly in many varied physiologic processes and especially in interspecies relationships (30). Therefore, it is possible that the metabolic processing of the injected gallium was orderly and took place in a physiologic manner. This need not imply that the mode of retention was absorption, ion exchange, or other mechanism, or that the excretion process in the kidney involved a renal threshold, was a secretory process, or damaged the tubules. On the other hand, it is unlikely that there are processes in the body specifically designed to deal with gallium.

Probably only the highest dose of gallium was in the pharmacologic or toxic range. The 25 mg. of gallium carrier per kilogram is about 10 per cent of the beginning of the lethal dose range, which is not too far above 220 mg. of gallium per kilogram (Section IV). No chemical signs of toxicity were observed except that this group of rats remained quiet for a day. Histologic evidence of damage to the viscera was absent.

According to the data on rats given large doses of gallium labeled with Ga^{72} (Section V), a rather good differential localization in bone was obtained by the fourth day after injection. The experiments in this report demonstrate that the differential was obtained by default of the other organs: All

the tissues other than bone retained relatively less of the metal at the higher doses of carrier. Prior to these experiments, it had been more or less tacitly assumed that the bone exhibited a special metabolic affinity for gallium. These data indicate that the process(es) responsible for the uptake by the liver, spleen, and similar organs had less capacity to handle high loads than did that for bone. The similarity of the slopes of liver, spleen, and femur at the low dose levels suggests that the process(es) of uptake, whatever it was, was not too different in these tissues. Shubert (31) has observed that non-specific biochemical reactions occur more frequently than is suspected, particularly when the material is present in concentrations of 10^{-6} molar or lower. This may apply to the uptake of gallium.

While it does not follow that the liver, spleen, and bone of man will show this carrier effect, the regularity of these rat data suggests that it is not restricted to the rat but is a physiological generality. Therefore, the clinical studies must be planned and conducted with this possibility in mind. The practical application of these experiments is that this factor, which may prove to be of critical importance for successful use of Ga⁶⁷ in man, would probably not have been suspected and identified in even the best clinical study.

In using Ga⁶⁷ to treat osteogenic and related neoplasms, an additional complication must be recognized. The neoplasm may or may not share in this segregating process, and it is possible that a given tumor may exhibit completely independent mechanisms for picking up or rejecting gallium and other substances.

In short, whether Ga⁶⁷ is differentially localized by osteogenic neoplasms can be determined only by assay in patients with such tumors, but the assay must be planned with provision for the carrier effect.

SUMMARY

The physical data necessary for biological and medical use of radioactive Ga⁶⁷ have been presented.

In a conventional tracer experiment on 32 rats with carrier-free Ga⁶⁷, the urine and feces contributed about equally to the 39 per cent excreted in five days. The femur, representative of bone, had a differential absorption ratio about 0.75 that of the spleen, while the liver lost much of the Ga⁶⁷ activity it had picked up initially. These data differed in several respects from those of comparable experiments in which the rats received milligram amounts of stable gallium^{69, 71} labeled with Ga⁷² (reported in Section V of this series).

In a succeeding experiment, the factor responsible for these differences was identified as the quantity of carrier or stable gallium administered to the animals. By controlling or keeping constant all factors except quantity of carrier gallium, it was found that the carrier-free pattern occurred when the dose of carrier was below 0.25 mg. of gallium per kilogram; above this level the pattern associated with high doses of carrier was obtained. A therapeutically desirable part of the latter experiments was a differential absorption ratio for bone which was ten to fifteen times higher than the second highest tissue. This difference was caused by a decreased percentage retention of the activity by the liver and spleen as the dose was increased, while the percentage retention of activity by the bone remained approximately constant.

Thus, these experiments suggest that stable Ga^{69, 71} may have to be added to the carrier-free Ga⁶⁷ preparations in order to secure the high differential concentrations of the radioisotopes in or around osteogenic neoplastic growth, but the question will have to be answered by experiments on patients suffering from such neoplasms.

ACKNOWLEDGMENTS: A large number of persons cooperated during the course of these experiments. Drs. Dana W. Nance, Robert R. Bigelow, and Paul Spray performed most of the surgery and contributed valuable consultant services. Many resident physicians from cooperating medical schools and the U.S.A.F. participated in the care and study of patients. Dr. Rex G. Fluhrty and Mr. Ralph H.

Ferminhac from the Special Training Division of the Institute and personnel from The Oak Ridge National Laboratories designed, constructed and, helped set up many of the instruments for radiation measurement. Valuable technical assistance was given by the following persons: Mary Bondurant, William Buher, Edgar Cress, Betty Ray Gray, Elmer Greene, Mary Gude, Eva Hodgins, Maryann Huddleston, Elmer Lea Keller, Helen Randolph, Melvin Russ, Robert Sellers, and Mary Smyser.

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SUMARIO

Estudio del Galio

Con todo pormenor preséntase este minucioso estudio del galio radioactivo (Ga^{72}), llevado a cabo por el personal directivo de la División Médica del Instituto Oak Ridge de Estudios Nucleares, de Oak Ridge, Tenn., E. U. A.

Estudiáronse las características físicas e

irradiatorias del isotopo e investigáronse, cuando poseían valor biológico, los aspectos químicos. La hemi-vida es de 14.3 horas, que se aproxima al límite inferior de la factibilidad para empleo clínico. Entre una gran cantidad de compuestos, el citrato de galio resultó ser el más aceptable.

Usáronse varias técnicas de preparación para adaptar el complejo citratado para empleo animal y humano.

Los experimentos de toxicidad general en ratas y perros revelaron una sensibilidad muy distinta conforme a especies. La DL 50 de diez días para ratas consecutivamente a la administración endovenosa fué de 220 mg. de galio por kilogramo de peso, comparado con una DL 50 en quince días de 18.2 mg. por kilogramo en los perros que recibieron las mismas preparaciones.

Los estudios en las ratas mostraron que el estado físicoquímico del compuesto de galio afectaba la distribución del metal consecutivamente a la inyección intravenosa. Al inyectarse en forma de complejo citratado soluble a un pH de 7.4, el hueso reveló la máxima absorción diferencial, aumentando esto durante un período de tres días. Ese diferencial favorable se debió a que el hueso absorbió inicialmente una fracción mayor de la dosis y la retuvo más firmemente que los tres tejidos que le siguieron en absorción, a saber, el hígado, el bazo y el riñón.

Consideróse que esas observaciones justificaban un ensayo clínico del complejo en el hombre, y más en particular en los tumores óseos, aunque no aportaban información relativa a qué dosis suministraría la absorción específica máxima compatible con la mínima toxicidad metálica e irradiación orgánica total.

En general, estudiáronse dos grupos de enfermos. En uno, tratóse abiertamente de producir un efecto terapéutico con Ga⁷². En el otro, no se hizo ninguna prueba terapéutica, sino que se estudió la localización o

absorción en los varios tumores o sitios. El radiogalio fué administrado intravenosamente a varias dosis a plazos de tres o cuatro días. Durante el tratamiento y después se ejecutaron frecuentes estudios hematológicos, se hicieron valoraciones de la radioactividad, se obtuvieron autorradiografías de los tejidos extirpados en la biopsia o autopsia y se verificaron los estudios histológicos de rigor. También se midió la excreción de galio en la orina y las heces.

Las manifestaciones más uniformes de toxicidad se relacionaron con el tubo gastrointestinal: anorexia, náuseas y vómito. Se observó una profunda depresión de la médula ósea, debida probablemente a la irradiación. Las reacciones cutáneas se imputaron a la toxicidad del estable galio. La distribución de éste en las lesiones óseas fué desigual, pero parecía existir tendencia a la localización en zonas de osteoactividad, ya osteoblástica u osteolítica. En general, aunque se administraron cantidades máximas del isótopo, hubo falta casi absoluta de toda mejoría clínica, si bien se observaron algunos signos de pasajero beneficio sintomático en enfermos que tenían metástasis carcinomatosas. No hubo ningún indicio del menor retardo del desarrollo de los sarcomas osteógenos, ya primarios o metastáticos.

Acompañanse relatos de los estudios de la excreción urinaria en el hombre y de los estudios autorradiográficos.

Completa el trabajo una reseña preliminar de los estudios experimentales realizados con el galio⁶⁷, que tiene una vida de 3.17 a 3.28 días.



Convergent Beam Irradiator

Apparatus for Convergent Beam Irradiation with Stationary or Moving Source¹

C. B. BRAESTRUP,² D. T. GREEN,³ and J. L. SNARR³

WHEN USING sources of high-energy gamma or x-radiation for teletherapy, it is necessary to provide a means of accurately positioning the beam relative to the patient. This may be done in a variety of ways. The choice of method usually involves some compromise between cost and utility. The most common method has been to provide a supporting framework for the source of radiation which allows one or more straight line motions in Cartesian co-ordinates and one or more rotational freedoms about an axis passing through or near to the source. Equipment has lately been designed which allows movement of the source in a centered arc of a circle on the tumor (1).

With the patient fixed, all required beam directions for deep therapy are provided by a source moving on the surface of a sphere, with the tumor at the center of the sphere and the beam directed radially inward to this center. Since the integral dose is considerably increased if the beam passes through the patient at a small angle to the long axis of the body, such beams should be avoided. The more useful beam directions are provided by a source moving on that portion of a sphere as illustrated graphically in Figure 1.

In general, it is preferable to orient beams by moving the source rather than the patient and to adjust the equipment until the beam of radiation is correctly aligned. Once this has been done so that the center of the tumor coincides with the center of the hypothetical sphere of source movement, one may use any number of different beam directions without further change in the position of the patient.

This sort of approach has led us to de-

sign the deep therapy equipment shown in Figure 2. The photograph reproduced is of the first installation at the Francis Delafield Hospital (New York) in May 1953.

GENERAL DESCRIPTION OF THE EQUIPMENT

The source of radiation for which this equipment was designed is a radioactive

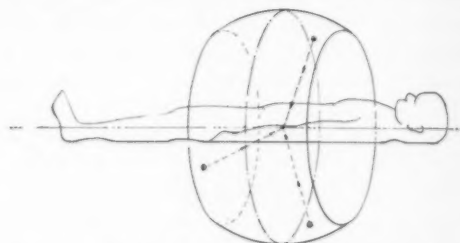


Fig. 1. Graphic illustration of beam directions obtainable with spherical source movements.

isotope delivering from 20 to 60 r per minute at 1 meter, of approximately 1.2-mev gamma radiation, which corresponds to about 3-million-volt x-rays. The cobalt-60 source used in the first equipment gives 18.7 r per minute at 1 meter. A protective housing for the source with a shutter to turn the beam on and off is mounted at one end of a curved arm. At the other end of this arm is mounted a combined counterweight and primary radiation shield, centered on the axis of the beam.

This assembly is supported on a horizontal shaft whose axis is 4 feet above floor level. The attachment between the curved arm and the shaft is such that relative movement is possible between them, the curved arm being capable of rotation in a limited arc, centered on the horizontal axis of the shaft, with the arc of movement ly-

¹ Presented at the Thirty-eighth Annual Meeting of the Radiological Society of North America, Cincinnati, Ohio, Dec. 7-12, 1952.

² Francis Delafield Hospital, New York, N. Y.

³ Atomic Energy of Canada Limited, Ottawa, Canada.

ing in the arm. This movement results in a circular planetary motion of the opposed source housing and shield-counterweight about the same point in space as the curved arm.

The horizontal shaft can be rotated to give a circular motion of the sources about

Light beams may be used to position the tumor on the center of the sphere defining the source movement. This may be done by providing two narrow opposing light beams, one from the shield-counterweight and one from the source housing, each coincident with the axis of the radiation beam.

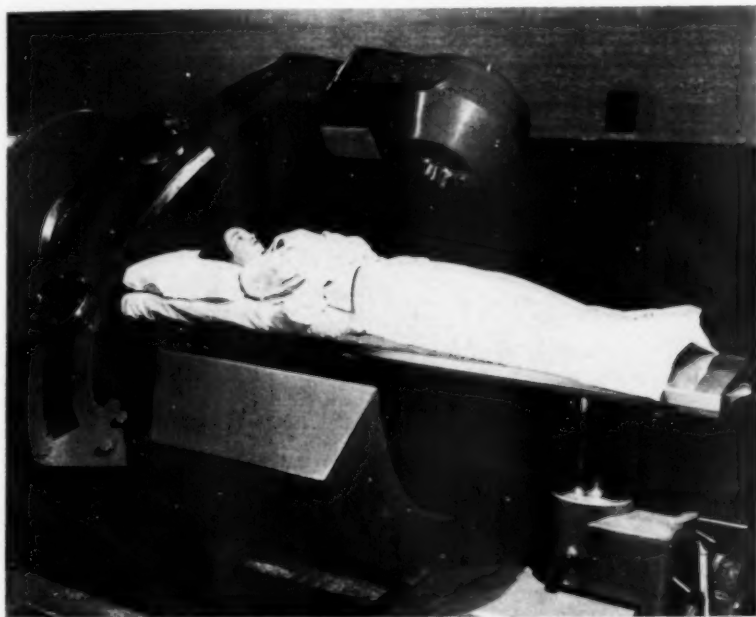


Fig. 2. First rotational cobalt-60 therapy equipment (installed at Francis Delafield Hospital).

its axis. The curved arm can also be moved relative to the horizontal shaft to tilt the plane of this circle from vertical to $22\frac{1}{2}$ degrees on either side of vertical. Both movements can be performed simultaneously, are reversible, and can be varied in speed. Mobility of the source is therefore obtained over an equatorial band of a sphere whose axis is horizontal. The beam of radiation is always directed inwardly along a radius of this sphere.

At the front end of the machine is a treatment couch supported on a framework which is an integral part of the equipment. Linear motion in three mutually perpendicular directions is provided in the treatment couch support. It is also possible to rotate the couch about a vertical axis near its front end.

After the tumor has been located and its position indicated by skin marks, the arm is placed in a horizontal position, and the treatment couch adjusted longitudinally and vertically to center the light spots on the skin marks. The arm is then rotated to a vertical position and the lateral shift of the couch is used to center on the other skin mark. The tumor is then at the center of source movement.

MULTIPORTAL THERAPY

Once the tumor is located on the center of source movement, a particular beam direction is defined by the angle shown on the scale of each rotational movement, and the orientation of the patient. A change in beam direction may involve moving the source to give a new angular reading on

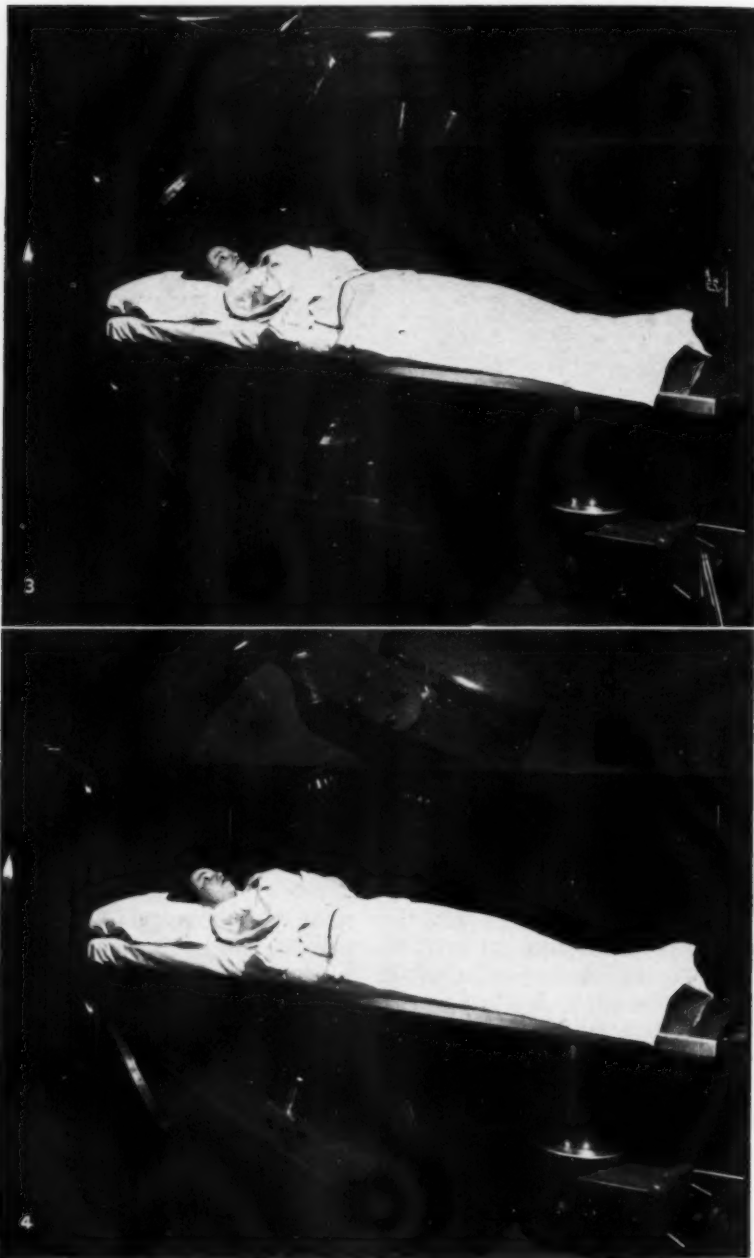


Fig. 3. Double exposure, showing rotation in a vertical plane.

Fig. 4. Double exposure, showing oscillation of curved arm over desired arc.

one or both of these scales. A series of beam directed treatments may be achieved without the operator leaving the control

area. This permits a higher work factor for the equipment and reduces the exposure to the operator.

ROTATIONAL THERAPY

The source movements available and the provisions made for supporting the patient during treatment are designed to permit rotational therapy. Since each of the two circular motions of the source is reversible, variable in speed, and controllable by limit switches and simple electrical signals, it is possible to describe many different configurations. A few examples follow:

Conventional Rotation:

- (a) Use horizontal shaft motion only, with circle of rotation in vertical plane. Rotate source at constant speed. See Figure 3.
- (b) Similar to (a), but use limit switches to reverse direction of motion at both ends of predetermined arc.
- (c) Use continuous rotation with limit switches to switch beam off and on at beginning and end of predetermined portion of each revolution.
- (d) Use curved arm movement to tilt beam from vertical to desired angle; then use continuous rotation, oscillation, or beam blanking. An isodose surface is thus produced by the beam generating a conical surface with its apex at the tumor.
- (e) Oscillate curved arm over desired arc, reversing automatically at each end of arc. See Figure 4.
- (f) Adjust couch on its vertical axis so that its length is at some angle to the main axis of rotation of the source, thus permitting rotation to be done with circle of rotation in a vertical plane at that angle to the longitudinal axis of the patient. See Figure 5.

Complex movements:

- (a) Use curved arm movement, reversing automatically at each end of travel; use continuous main rotation simultaneously. The source then describes a sawtooth or sine wave motion in a circular band about the tumor.
- (b) Make one movement over short arc, then move by second motion over



Fig. 5. Tilted circle of rotation by couch angulation. Scale model.

equal arc, then reverse first motion, and repeat cycle. The axis of the beam generates a pyramid with its apex at the center of source movement. By decreasing the arcs of movement at the end of each cycle, the pyramid's angle decreases and the source moves in what might be called a "square spiral" path.

- (c) Make each motion a simple harmonic movement, with equal amplitude and frequency, but out of phase. The source then describes a circular path and the beam axis generates a cone. Variations in phase, amplitude, and frequency between the two movements of the source make the source describe ellipses, figure eights, and various other Lissajou figures.
- (d) Use continuous rotation on the main axis, oscillate the curved arm so that it reverses twice during the main rotation. This gives a "tilted circle" rotation similar to that obtained by setting the treatment couch at an angle to the main axis of rotation, except that the plane of the circle need not necessarily be vertical.

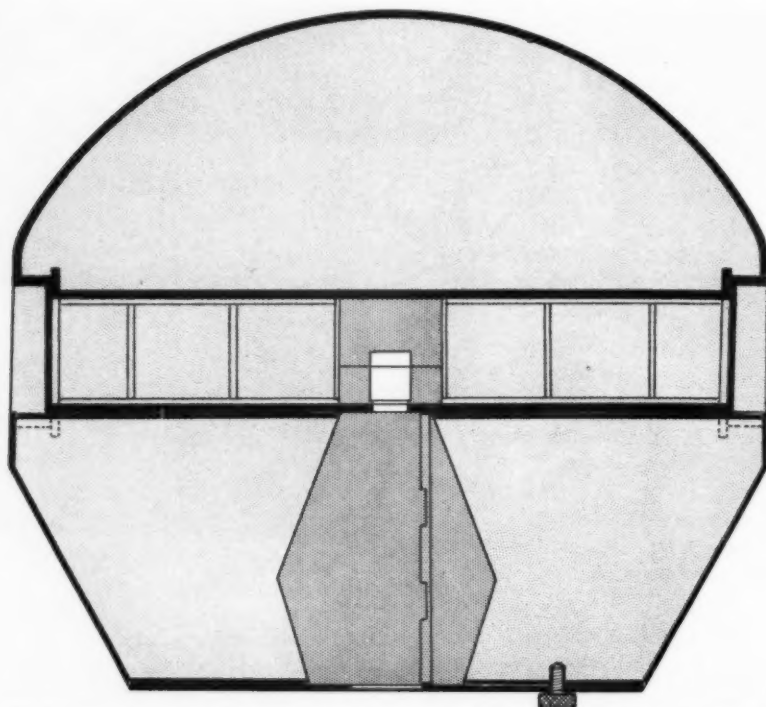


Fig. 6. Source housing, including source drawer, sliding block type shutter, and tungsten alloy shielding around source.

CONSTRUCTION DETAILS

The source housing is a combination of lead and tungsten alloy shielded in a steel case with welded closures (Fig. 6). Enough tungsten is used to reduce the distance from the source to the bottom of the housing to the minimum possible with this material. This is important, since the maximum clearance provided between the housing and the couch and patient determines the arc of motion possible for the curved arm. Calculations of the thickness of lead and tungsten alloy required for a large number of beam directions in two planes made it possible to draw a theoretical outline of the tungsten alloy required (Fig. 7). This was then approximated by a simple shape.

In order to reduce to some extent the weight of the housing, about two half-value layers of tungsten are provided around the source in all other directions. This shield is designed to reduce the radia-

tion to approximately 6.25 mr per hour at its outer surface at all exposed points, with a 20 r per minute at 1 meter Co^{60} source. The rate of 6.25 mr per hour corresponds to the present maximum permissible exposure of 300 mr per week, assuming forty-eight hours uniform weekly exposure. The source container, loading, shipping, and installation methods have been described elsewhere (2).

The shutter is a sliding block type with stepped sliding surfaces to reduce scattered radiation leakage, as shown in Figure 8.

The aperture system is non-adjustable, due to space limitations, but various sizes of apertures giving fields from 5×5 cm. to 15×15 cm. may be readily inserted or removed. An extension tube enables the source-to-aperture distance to be increased to reduce the penumbra for treatments where the maximum clearance between the aperture and the center of source movement is not required. The heaviest

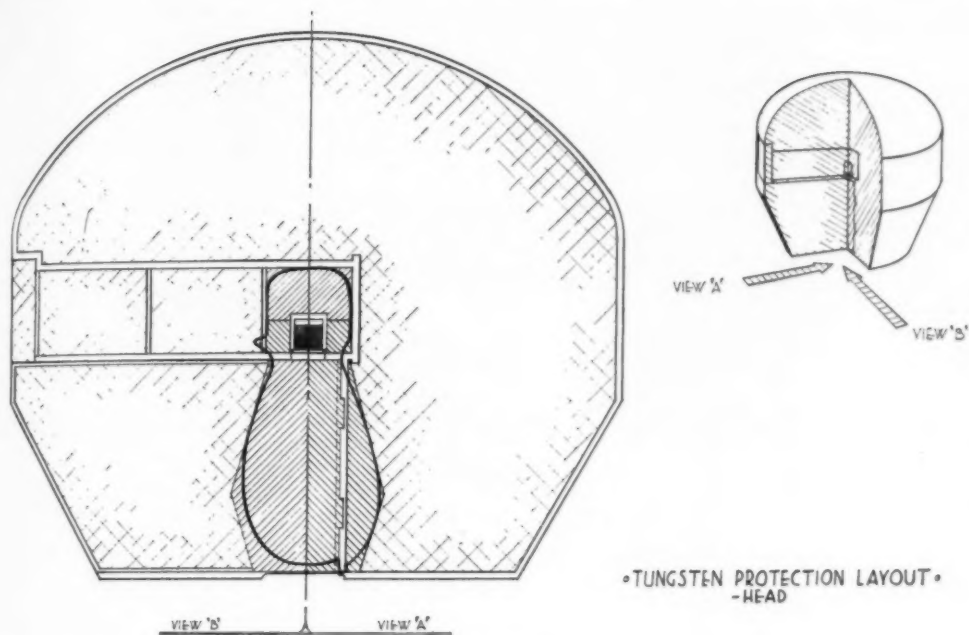


Fig. 7. Tungsten alloy shielding.

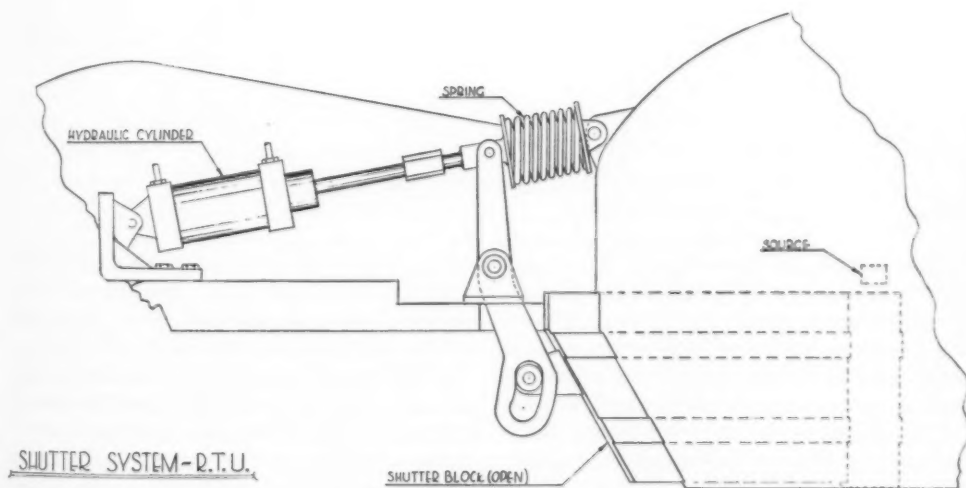


Fig. 8. Shutter system. The shutter opens against a strong spring which supplies the closing force should the hydraulic system fail.

removable aperture weighs less than 9 lb. The aperture can be rotated 360 degrees about the axis of the beam. Tungsten alloy is used for the apertures to decrease

their length along the axis. Figure 9 shows the construction of the diaphragms and the penumbra with and without extension tube. Figure 10 shows the two motor drives

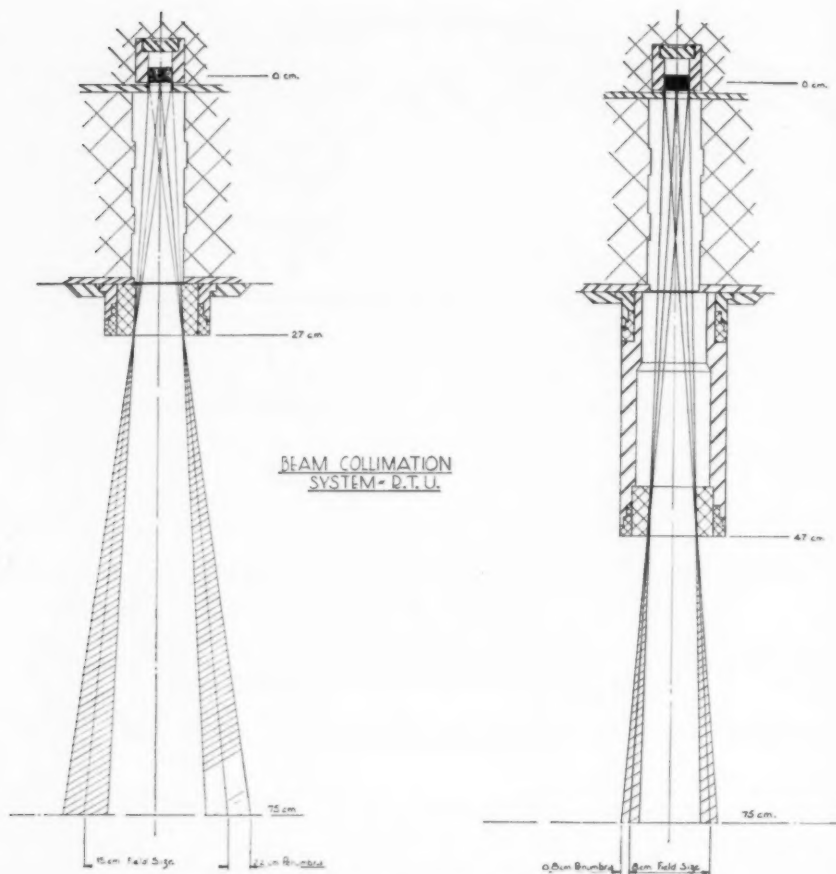


Fig. 9. Collimating system.

for the motion of the source. The main shaft is connected to a synchronous transmitter which indicates movement and position by means of a receiver on the control panel. A hand control located in the treatment room and connected by flexible cable to the motor controllers enables adjustments to be conveniently made during set-up.

The treatment couch is a 3/16-inch sheet of aluminum reinforced at the edges with aluminum bars which serve also as the tracks upon which the couch rolls longitudinally. For fixed beams the couch can be lowered to 120 cm. below the center of the source. An electrically operated hydraulic cylinder provides the vertical move-

ment, while rotation and horizontal movements are manual. All movements may be locked with brakes and carry graduated scales. Figures 11, 12, and 13 illustrate the wide range of motions possible with the couch. Figure 14 shows the position of the couch when the patient gets on or off.

It is necessary to provide safeguards against accidental collision of the head, arm, or counterweight with the patient or the treatment couch. This is accomplished by having the couch top and the patient electrically connected and insulated from the remainder of the mechanism. They constitute one plate of a capacitor, and the balance of the machine forms the other. This capacitor is in the resonant

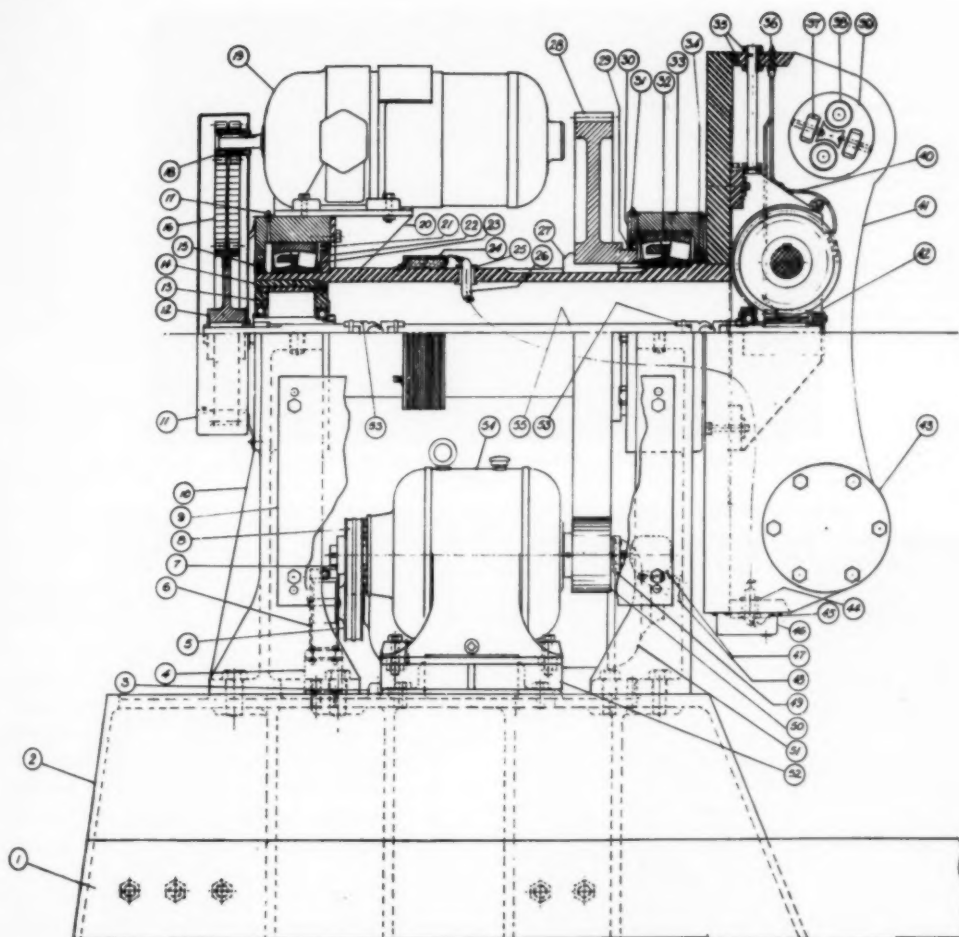


Fig. 10. Motor drives for source rotation and oscillation.

circuit of an oscillator and, if any moving portion of the machine comes closer than approximately 1 inch to the patient or treatment couch, the current change in the plate circuit of the oscillator operates a relay which instantly brings all movements to a stop.

The control panel allows speed indication and control of the main rotation movement. Speed indication is provided by an a.c. voltmeter with a scale, calibrated in r.p.m., which is connected to the alternator on the output shaft of the eddy current clutch of the motor. Speed control is accomplished by a potentiometer setting

which regulates the slip in the eddy current clutch. Position is indicated by a synchronous receiver coupled to the transmitter on the drive motor, and is controlled by forward and reverse pushbuttons.

The position indicator for the main drive is arranged so that it can operate two independent micro switches at any preselected point during a revolution. These two switches may be used to reverse the motion at each end of a particular arc, or they may be coupled into the shutter mechanism to turn it on and off. The choice of operation is dictated by whether the arc over which one wishes to treat is greater or less than

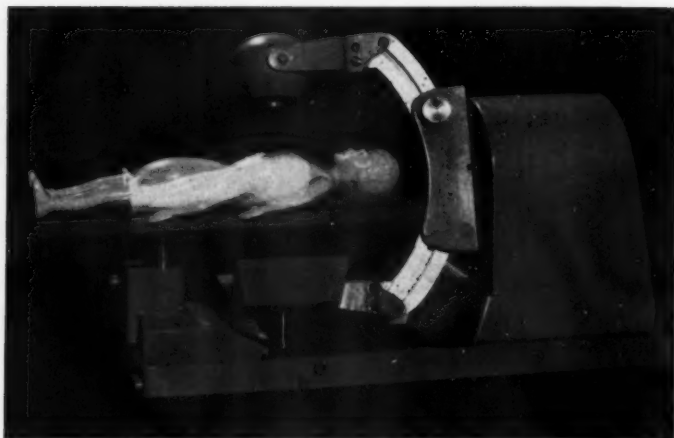


Fig. 11. Double exposure, showing longitudinal motion of couch. Scale model.



Fig. 12. Triple exposure, showing transverse motion of couch. Scale model.

180 degrees, since in general less time is consumed by reversing rotation over arcs less than 180 degrees, and by blanking out the beam over the untreated arc if the treated arc is to be greater than 180 degrees. The choice of operation method is controlled by a switch on the control panel. A time switch is provided to control the total time the shutter is on, and to shut the machine down when that time has elapsed. Pilot lights show when the beam is on or off and indicate stoppage due to incipient collision.

FUTURE POSSIBILITIES

It is apparent that since the direction and speed of each motion may be controlled by supplying the proper D.C. voltages to the motor control circuits, it would be relatively easy to generate voltages of varying polarities and magnitudes, properly phased with respect to each other, so that combinations of the two source motions to accomplish the more complex rotations previously mentioned could be arranged. It is also possible that, by feeding the right type of information, in the form of electrical signals, into the motor controllers, one could create an isodose surface of almost any desired shape within the patient. With a three-dimensional cam controlling rate of rotation, oscillation, and perhaps mechanized longitudinal couch motion, something approaching fully automatic treatment is possible, in that an ideal isodose surface for the individual case could be automatically generated. A host of possibilities crowds into mind which no doubt cannot be sensibly evaluated without the benefit of considerable experimentation and clinical experience with the equipment.

SUMMARY

An equipment is described where a source of radiation may be freely moved over a large part of the surface of a sphere, with



Fig. 13. Double exposure, showing vertical motion of couch. Scale model.



Fig. 14. Position of couch while patient is getting on or off.

the beam of radiation always directed at the center of the sphere. Once a patient is fixed in position with the center of the tumor coinciding with the center of the sphere which defines the motion of the source, the beam is always pointed at the tumor, irrespective of the position of the source.

The change of treatment fields requires

only one motion of the source without moving the patient, thus facilitating set-up and reducing the possibility of errors in positioning. Since the spherical motion of the source is accomplished by permitting simultaneous motion on two arcs in planes at right angles to each other, a degree reading on the two arc scales defines uniquely the direction of the beam.

Because the source movement over the surface of the sphere is accomplished by reversible electric motors whose speed can be varied, rotational therapy of many types may be accomplished. The possibility of a wide variety of configurations of the source in its spherical movements enables considerable control over the shape of the isodose field in the patient.

The treatment couch is an integral part of the equipment and is designed to facilitate set-up and to allow a wide choice of treatment methods.

The control equipment makes possible rotation of the source over a predetermined arc, with independent control of the arc over which the radiation is emitted. Control equipment to enable predetermined isodose fields to be built up within the patient is a possible future development.

ACKNOWLEDGMENTS: There are many persons to whom acknowledgments are due, but space permits mention of only a few. Among radiologists, Drs. V. Collins, J. T. Nickson, T. C. Pomeroy, I. H. Smith, and T. A. Watson have all contributed worth-while suggestions. Very useful ideas and assistance have been offered by G. Ferlazzo, E. F. Fecht, and by many of the engineers and physicists of Atomic Energy of Canada Limited, particularly Mr. R. F. Errington.

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SUMARIO

Irradiador de Haz Convergente: Aparato para Irradiación de Haz Convergente con Foco Estacionario o Movable

La instalación descrita permite mover sin dificultad un foco de irradiación sobre una gran parte de la superficie de una esfera, con el haz de rayos apuntando siempre al centro de la esfera. Una vez fijo el enfermo en posición, con el centro del tumor por tratar coincidiendo con el centro de la esfera que define el movimiento del foco, el haz apunta siempre al tumor, independientemente de la posición del foco.

La alteración de los campos terapéuticos no requiere más que un movimiento del foco, sin mover al enfermo, facilitando así los arreglos y reduciendo la posibilidad de cometer errores al colocar al sujeto en posición. Como el movimiento esférico del foco se realiza mediante el movimiento simultáneo sobre dos arcos dispuestos en planos en ángulos rectos entre sí, la lectura de los grados en las escalas de los dos arcos define en forma única la dirección del haz.

Por ejecutarse el movimiento del foco sobre la superficie de la esfera por medio de motores eléctricos reversibles, cuya velocidad es ajustable, cabe aplicar terapéutica de muchas formas. La posibilidad de obtener una amplia variedad de configuraciones del foco en su movimiento esférico permite ejercer mucho dominio sobre la forma del campo de isodosis en el enfermo.

La camilla de tratamiento forma parte integrante de la instalación, estando destinada a facilitar los arreglos y a permitir una amplia selección de técnicas terapéuticas.

El mecanismo de gobierno permite la rotación del foco sobre un arco predeterminado, con gobierno independiente del arco sobre el cual se emite la irradiación. Un posible desenvolvimiento del futuro es un mecanismo de gobierno que capacite para organizar en los tejidos del enfermo campos predeterminados de isodosis.

Radiation Hazards from the Use of Dental X-Ray Units¹

W. E. NOLAN, A.B., and H. W. PATTERSON, A.B.

FOR MANY YEARS x-rays have been used in the dental profession as a diagnostic tool. X-rays cannot immediately be felt or seen, and therein lies the hazard attending their use. What cannot be sensed is often ignored and, through unconcern and neglect, an exposure resulting in biological impairment or damage may result. It was for this reason that an investigation of the potential hazard occurring during dental roentgenography was undertaken.

INSTRUMENTS AND TECHNICS

The primary standard employed to measure x-ray dosages in the voltage range common in dental practice (50-75 kv.) was the Victoreen condenser r-meter and thimble chamber. To supplement these measurements, two types of special monitoring film (Dupont No. 552 and No. 558), as well as a portable ionization chamber, were used. The density of the test exposure film was compared directly with the density on standard exposure films by means of a Photovolt densitometer.

All dosages or dosage rates are expressed in roentgens (r). The presently accepted tolerance dose of x or gamma radiation is 0.3 r per week (1), specifically excepting possible genetic effects².

HAZARD TO DENTISTS AND TECHNICIANS

Radiation survey results are shown below for six dentists' offices in this area. Radiation dose rates refer to the condition existing when the voltage and current values were those most commonly used.

Office Number 1: The operator in this office was exposed to x-radiation in excess of 1.2 r/hr.

Office Number 2: The operator in this office was exposed to radiation in excess of 0.2 r/hr. The receptionist was exposed to radiation in excess of 0.06 r/hr.

Office Number 3: The operator in this office was exposed to radiation in excess of 1.5 r/hr. (In this case, recommendations were carried out, and a resurvey showed an exposure of between 0.001 and 0.003 r/hr.)

Office Number 4: In this office the operator was exposed to radiation in excess of 0.2 r/hr. The walls of the office were portable and very thin. Radiation in excess of 0.2 r/hr. was also received in the next office.

Office Number 5: It was found that the operator was exposed to radiation in excess of 1.2 r/hr. This was a small but very busy office and one of the most hazardous of those surveyed. Recommendations were made and steps were taken to shield the operator.

Office Number 6: In this office, a very small one, the operator was found to be exposed to radiation in excess of 2.0 r/hr. The receptionist was exposed to more than 0.04 r/hr.

In general, monitoring films worn by dentists and technicians who made only moderate use of their x-ray equipment showed less than tolerance blackening. Occasional overexposure may result, however, no matter how little the x-ray equipment is used. In one instance, after a dental technician had worn a film for a period of one week, the resultant density was so great that the film could not be read on the densitometer. This would correspond to an exposure in excess of 5 r, or more than seventeen times the maximum permissible weekly exposure.

Discussion: It can be seen that these six offices, assumed to be typical, presented hazards in a greater or lesser degree. The fact that the operator is exposed at all indicates the advisability of taking every reasonable precautionary measure.

¹ From the Radiation Laboratory, University of California, Berkeley, Calif. Accepted for publication in November, 1952.

² This corresponds to a continuous dose rate during a forty-hour work week of 0.075 r/hr.

In general, most of the hazards were removed by the use of (1) proper shielding, (2) collimation of the x-ray beam, (3) filtration of the x-ray beam, (4) safer physical positions for the x-ray tube and the operator.

The first and fourth of these measures might consist in the construction of a semi-permanent screen of 1/16 inch sheet lead, through which a lead glass viewing port is cut. A few additional feet of x-ray machine timer cord would be necessary to allow the operator to stand behind the screen. Collimation should absorb that portion of the x-ray beam that cannot be utilized to expose the dental x-ray film, while filtration with 1.0 or 2.0 mm. of aluminum actually improves the quality of the x-ray pictures by absorbing the easily scattered, fog-producing, low-voltage x-rays.

It is probable that all dental offices should be routinely monitored to prevent development of a radiation hazard. Certainly, at the time of installation of equipment an adequate survey should be made. In the event that this has been overlooked, one should be made by a competent health physicist, comprising the following steps: (1) survey with an air ionization chamber, film, and Victoreen r-meter; (2) report and recommendations for shielding and any other necessary steps; (3) resurvey and complete report of corrected conditions.

A few remarks are in order with respect to the dangers involved when a dentist or technician holds a film in position while making an exposure. This practice is not only extremely dangerous but entirely unnecessary, and repeated performances might result in damage to the hand used. Fortunately, this type of injury is on the decline, due in part to conditions that now prevail in the dental profession. First, and most important, is the fact that with few exceptions the present-day dentist has been properly indoctrinated with respect to this hazard. Second, modern equipment, methods, and techniques have contributed in a large meas-

ure toward eliminating this type of injury. But, though its incidence is lower today than in the past, the potential hazard is always present. With this in mind, the dentist must be ever vigilant if injuries of this nature are to be completely eliminated.

HAZARD TO THE PATIENT

Upon visiting a dentist for preliminary examination, the patient in most instances is subjected to a "full-mouth" x-ray examination. This may entail the taking of fourteen to thirty-five radiographs, depending on the technic used.

The amount of radiation delivered to the patient depends on several factors, as follows: (1) the energy of the x-rays, (2) the focal distance (distance between tube target and skin), (3) the amount of filtration, (4) the amount of current, and (5) the total time of exposure.

The energy of the x-rays is important, as it is the major factor in determining the rate at which the radiation is being delivered and also in determining the depth of penetration. In most cases, the higher the energy, the greater the rate of delivery, and, of course, the greater the energy, the greater the depth of penetration.

In general, there are two focal distances in use. One technic employs an 8-inch focal distance, the other a 16-inch focal distance. With the 8-inch distance, the exposure time is shorter than with the 16-inch distance, but the total amount of radiation delivered to the patient can be as high as three to four times that which is delivered when the longer focal distance is used. One might think that the dose to the patient would be the same in both cases and that the exposure time with the 8-inch distance should be one-fourth that with the 16-inch technic. This is not the case. In most instances, the total exposure time with the 8-inch technic is only about 35 per cent less than with the 16-inch technic.

The amount of filtration is very important. In many instances no filtration is used with dental equipment. Failure to

filter out all soft radiation increases the dose tremendously.

Most machines examined in this study were operated with a current of 10 ma.

The total time of exposure for a full-mouth examination varies, depending on the technic employed. It can be as little as 50 seconds and may be as long as 1 minute 35 seconds. This is no doubt the most important factor in determining the total dose received by the patient.

Films were used to determine the dose delivered to various anterior and lateral surfaces of the face, neck, and chest. Films were placed in contact with the patient's neck, completely surrounding it. In addition, films were placed at twelve locations on the anterior surface of the body between the neck and the waist. This technic was used on three patients, and the films were read on a Photovolt densitometer against a previously run set of film standards. The measurement pertaining to the rate at which the dose is delivered was repeated several times in all cases.

DENTAL MACHINES EXAMINED AND RESULTS OBTAINED

Thirty-two dental units, assumed to be typical, were examined in the San Francisco Bay area. The following data were collected from three of these units, the findings varying with the machine and the technic used.

Machine A: This machine was operated at 65 kv., 10 ma., with no filtration, at a 16-inch focal distance. The number of exposures for a full-mouth examination averaged about thirty. The total time of exposure was about ninety seconds. The rate of delivery was 75 r/min., or a total of 113 r delivered to the face and neck area during the complete examination.

Machine B: This machine was operated at 45 kv., 10 ma., with no filtration, at an 8-inch focal distance. The number of exposures for a full-mouth examination was about twenty-five. Total exposure time was about seventy seconds. The rate of

delivery was 270 r/min., or a total of about 315 r to the area during the full-mouth examination.

Machine C: This machine was operated at 65 kv., 10 ma., with no filtration, at an 8-inch focal distance. The number of exposures for a full-mouth examination was about twenty-eight, and the total exposure time was about seventy-five seconds. The rate of delivery was 190 r/min., or a total of about 238 r delivered to the area during the examination.

An examination of Machine B was made after a filter of 2 mm. Al had been installed, all other operating conditions remaining the same. The rate of delivery was found to be 40 r/min. as compared to 270 r/min. without filtration. The radiographs were of much finer quality, owing to the fact that much of the softer radiation that tends to fog the film was now eliminated.

In none of the three cases in which film was used to measure the dosage to various lateral and anterior surfaces of the body, did the dose delivered to any area below the shoulder line exceed 2 r. In the region of the face and neck the dose was much greater, in excess of 75 r to both lateral surfaces and somewhat less to the anterior surface.

In the region of the neck there is a large amount of lymphatic tissue. This tissue is exceedingly sensitive to radiation (2, 3) and, with the high dose rates observed, changes in the blood picture of patients undergoing such examinations might be expected.

Hematological studies are being carried out at the present time on a group of patients who have undergone full-mouth dental radiography, and the results of these studies will be reported in a future paper. For the present, it can be said that significant blood changes have been observed in patients exposed to full-mouth radiography.

Discussion of Results: It is apparent from the above data that a considerable amount of radiation is absorbed by the patient during dental x-ray examinations.

The exposure is not confined to the area being radiographed but extends over a much larger area. It has also been shown that very good radiographs can be obtained without exposing the patient to excessive radiation. It should be pointed out that the total amount of radiation received by the patient is delivered to an area embracing the entire jaw and neck and in many instances including areas below the shoulder line. To any 1 sq. cm. of skin surface the dose will in most cases not exceed 100 r. There are however, many intersecting lines of radiation within the neck and oral cavity, due to the angle at which the radiographs are taken. These points of intersection are definitely points of greater ionization.

SUMMARY AND RECOMMENDATIONS

In the future the use of x-rays as a diagnostic tool will certainly increase rather than decrease, in both the medical and dental professions. In view of this trend, it would seem important that the dentist give careful consideration to all factors involved when ordering full-mouth radiography. The patient should be questioned with respect to prior x-ray examinations of any nature, since present thinking (4) is that ionizing radiation of all types has a cumulative biological effect.

It is entirely possible that a patient could be undergoing a radiographic examination of some other portion of the body during the same period that oral roentgenography is being performed. To keep the x-ray exposure to a minimum, it would be wise for the dentist to consider this possibility before ordering full-mouth radiography.

Personnel who presumably will be engaged for many years in a profession necessitating work with ionizing radiations and radioactive materials should have a compelling indication before full-mouth radiography is carried out.

Other points that should be mentioned are the following: A patient could con-

ceivably be exposed several times to a full-mouth x-ray examination within a short period of time. In many cases, the entire upper portion of the body is bathed in radiation to a greater or lesser degree.

A record of exposure should be kept for all persons undergoing x-ray examination of any type.

All personnel whose profession requires them to use x-ray equipment of any kind should be completely familiar with the equipment they use with respect to kilovoltage, current, filtration, if any, and the output of the unit.

Several recommendations are in order at this point with respect to the dental unit itself.

1. All dental units should be equipped with proper filtration.
2. The x-ray beam should be collimated so as to cover precisely the area to be radiographed.
3. A long focal distance should be used at all times.
4. The shell housing the tube should be x-ray-proof. (Many in use at the present time are not.)
5. It might be profitable to investigate some new film technics, such as impregnating the emulsion with a material that would fluoresce upon being irradiated. A piece of calcium tungstate might be included as an integral part of the film packet.
6. It might also be worth while to consider a shield of some sort to protect the patient's neck from secondary and scattered radiation.

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SUMARIO

Riesgos de la Irradiación al Emplear Aparatos Dentales de Rayos X

Estudios de la irradiación efectuados en seis consultorios odontológicos, considerados como típicos, revelaron más o menos peligro para los operadores de los aparatos de rayos X. Además, se inspeccionaron treinta y dos aparatos odontológicos para determinar la exposición del enfermo, sobre todo al ejecutar exámenes de toda la boca. Esa exposición no se limita a la zona que se radiografía, sino que abarca una región mucho mayor. Las dosis altas aplicadas a los tejidos linfáticos sensibles del cuello provocan alteraciones importantes del cuadro sanguíneo, con depresión de la fórmula linfocítica.

Ofrécense recomendaciones para la

protección tanto del personal técnico como de los pacientes. Con respecto a los aparatos odontológicos mismos, aconsejase que estén provistos de filtros adecuados; que se colime el haz de rayos X para que abarque precisamente la zona por radiografiar; que se utilice una distancia focal larga; y que el mueble del tubo no deje pasar los rayos. Sugíerese además que se investigue alguna nueva técnica para películas, como la impregnación de la emulsión con una substancia que fluoreszca al ser irradiada, y que se piense en la obtención de una pantalla de algún género que proteja el cuello del enfermo contra la irradiación secundaria y esparcida.



Abdominal Aneurysm as an Uncommon Cause of Duodenal Loop Widening¹

BRIT B. GAY, JR., M.D., TED F. LEIGH, M.D., and JAMES V. ROGERS, JR., M.D.

WIDENING OF THE duodenal loop is a well recognized sign in pancreatic disease. It is also present in association with masses of other types in the region of the head of the pancreas, as emphasized in standard texts on gastrointestinal radiology (2, 4, 6). Aneurysm of the abdominal aorta has been mentioned briefly as a cause of duodenal displacement, but widening of the duodenal loop from this cause, simulating pancreatic cyst or carcinoma, has not been stressed. Poppel's monograph (6) gives the impression that such widening does not occur with abdominal aneurysm.

During the past two years we have seen 3 patients with marked widening of the duodenal loop due to abdominal aortic aneurysm, closely simulating the defects associated with pancreatic cyst or carcinoma without invasion of the duodenum.

CASE I: H. R. G., an 81-year-old white woman, complained of abdominal pain, weakness, and indigestion. Eight to ten years before admission she began having attacks of indigestion. About four years later abdominal pain occurred, radiating to the back and down the left leg. During the past six months weakness and anorexia had increased, abdominal distention had developed, and the pain had become more severe. The past and family histories were non-contributory.

Physical examination showed evidence of weight loss. High in the epigastrium was a hard, slightly irregular, fixed mass, which did not move on inspiration. No bruit was present. A provisional diagnosis of carcinoma of the pancreas was entertained.

Radiologic studies of the lumbar spine and gastrointestinal tract revealed a large mass in the region of the head of the pancreas, causing widening of the duodenal loop. About the periphery of the mass curvilinear calcification was demonstrated. The abdominal aorta showed considerable arteriosclerotic change. Laminagraphic studies localized the mass to the area of the aorta. In the spinal films there was no evidence of vertebral erosion. The thoracic aorta showed extensive arteriosclerotic change with tortuosity and dilatation (Fig. 1).

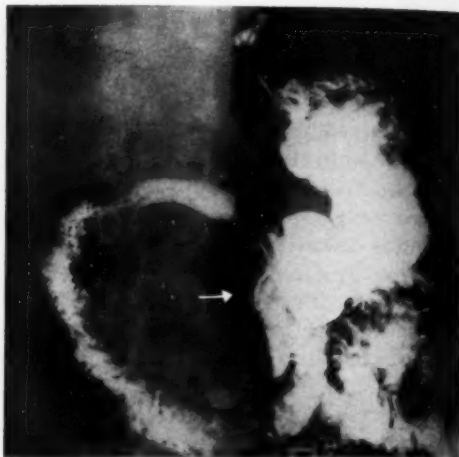


Fig. 1. Case I. Postero-anterior view showing marked widening of duodenal loop and extrinsic pressure upon the greater curvature of the gastric antrum due to abdominal aortic aneurysm. Arrow points to calcification in the aneurysmal wall.

Final Diagnosis: Large aortic aneurysm creating widening of the duodenal loop and compressing the greater curvature of the antrum.

Because of the patient's age, it was felt that further therapeutic procedures were not warranted.

CASE II. L. M., a 69-year-old white male, first noticed a mass in the epigastrium a few months before admission. During the past month he had become quite anxious, believing himself to have a cancer. His anxiety led to anorexia, with a weight loss of some 20 pounds. About six months before admission, he had had what was diagnosed elsewhere as a "virus infection" of the lungs. There had been no vomiting or bloody stools.

Physical examination showed a generalized dermatitis and atrophy of the papillae of the tongue, which were interpreted as representing an avitaminosis. A large pulsating abdominal mass was felt. This was quite hard and was fixed in position.

A gastrointestinal series revealed no intrinsic abnormality of the esophagus or stomach. The duodenal loop was markedly widened and the area enclosed by it corresponded to the palpable mass. The immediate films demonstrated peripheral calcium deposits distributed in a curvilinear fashion through the mass (Fig. 2).

¹ From the Department of Radiology, Emory University Hospital and School of Medicine, Emory University, Georgia. Accepted for publication in November 1952.

Diagnosis: Abdominal aortic aneurysm creating widening of the duodenal loop and simulating a pancreatic cyst or carcinoma.

CASE III: Mrs. J. McM., an 87-year-old white female, had suddenly vomited a large amount of tarry material on the morning of admission. A similar episode had occurred three days previously, but was much less severe. The family physician, who found the patient to be in mild shock, referred her



Fig. 2. Case II. Postero-anterior view showing widening of duodenal loop by aortic aneurysm. Note curvilinear calcium deposit (C) in aneurysm wall within duodenal loop. A duodenal diverticulum (D) is also present.

to Emory University Hospital. The past and family histories were non-contributory.

The blood pressure was 140/40; respirations 20; pulse 104. A large pulsating mass was noted in the central portion of the abdomen. Pedal pulsations were normal.

Laboratory studies revealed 3,200,000 red blood cells, 9.9 grams of hemoglobin with a hematocrit of 32 mm. The sedimentation rate was 47 mm. in an hour. The white blood count was normal. A serologic test for syphilis was negative. Examination of the vomitus revealed a 4-plus guaiac reaction.

Presumptive diagnoses of bleeding peptic ulcer and probable aortic aneurysm were made.

Radiologic studies of the upper gastrointestinal tract revealed a smooth widening of the duodenal loop and mild elevation of the gastric antrum (Fig. 3), due to a large pulsatile abdominal mass, which was easily palpable. On the immediate films faint



Fig. 3. Case III. Widening of the duodenal loop by an abdominal aneurysm, as seen in postero-anterior view. In the original film faint calcifications could be seen in the wall of the mass.

calcifications could be seen within the margin of the mass. There was a moderate prolapse of the antral mucosa into the base of the duodenal cap.

The patient was treated with sedation, an ulcer regimen, and multiple transfusions. Surgical intervention was not considered desirable.

Final Diagnosis: Large abdominal aneurysm causing widening of the duodenal loop and compression along the greater curvature of the gastric antrum.

DISCUSSION

The differential diagnosis of lesions in the region of the head of the pancreas preoperatively or antemortem may be difficult. It is well recognized that there are many causes for compression and widening of the duodenal arc. The most common lesions have been tabulated by Rendich, Poppel, and Cove (7), in order of importance, as follows:

- (1) Carcinoma of the head of the pancreas
- (2) Enlargement of lymph nodes in region of pancreatic head, due to
 - (a) Lymphoma
 - (b) Metastases
 - (c) Inflammatory disease (tuberculosis, infectious mononucleosis)
- (3) Edema of the pancreas in biliary disease
- (4) Chronic pancreatitis

- (5) Other retroperitoneal tumors, as sarcomas
- (6) Cysts of the head of the pancreas
- (7) Aneurysms of the anterior wall of the abdominal aorta
- (8) Amyloidosis of pancreas
- (9) Upward traction on the duodenum as in hiatus herniation of the stomach.

Clinically, differentiation of pancreatic carcinoma, pancreatic cyst, and abdominal aortic aneurysm is frequently difficult on the basis of the physical signs. Palpable pulsations may be absent in aortic aneurysms and transmitted pulsations from a normal aorta through a pancreatic mass may simulate aneurysm.

Radiologic examination in most cases will permit differentiation of vascular and non-vascular lesions in the region of the head of the pancreas. Routine abdominal roentgenograms will show the presence of a soft-tissue mass with curvilinear peripheral calcifications and occasional vertebral erosion and will allow a diagnosis of aneurysm in most cases, as, for example, in 85 per cent of Estes' 102 patients (3). Vascular lesions can be definitely excluded by aortography.

The duodenal loop is apparently not frequently affected by aneurysm. In Scott's series (8) of 96 abdominal aneurysms, none showed compression of the duodenum. Hubeny and Pollack (5), in their series of 48 aneurysms of the abdominal aorta, found one case with compression of the duodenum and antrum of the stomach similar to the cases reported here. Baird and Kirklin (1) described a case of duodenal obstruction due to abdominal aortic aneurysm. In Estes' series of 102 cases of abdominal aortic aneurysm, only one showed duodenal compression.

In spite of the rarity of aneurysm as a cause of widening of the duodenal loop, it should be given consideration in the differential diagnosis of lesions of the head of the pancreas.

SUMMARY

Aneurysm of the abdominal aorta should be considered in the differential diagnosis of masses in the region of the head of the pancreas.

Widening of the duodenal loop such as occurs with pancreatic neoplasm and cysts may be produced by aneurysm of the abdominal aorta.

Three cases of abdominal aortic aneurysm which produced marked duodenal loop widening are presented.

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SUMARIO

Los Aneurismas Aórticos como Causa de Dilatación del Asa Duodenal

El ensanchamiento del asa duodenal como signo de afección pancreática está bien reconocido. Esa asa puede también ensancharse cuando existen tumefacciones de otros géneros en la región de la cabeza del páncreas. Preséntanse aquí 3 casos en

los que dicha dilatación se debía a un aneurisma de la aorta abdominal, haciéndose notar que debe considerarse este último estado en el diagnóstico diferencial de tumefacciones presentes en la región de la cabeza del páncreas.

An Oral Cholecystographic Method Using Telepaque with Demonstration of the Common and Cystic Ducts¹

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THE SEARCH FOR an ideal cholecystographic medium has been directed toward a drug with fewer side-reactions and better concentration than were associated with those used in earlier studies (7, 8, 11). Little improvement was obtained, however, until twelve years ago, when iodoalphonic acid (Priodax) was introduced (10). This was far superior to other media tried but fell short of the ideal in several respects. While the side-reactions were rarely severe, they were still much too frequent and always annoying. They were found by various investigators in 40 to 90 per cent of patients examined (1, 6, 9, 13, 14). Coupled with these objectionable reactions were poor concentration and delayed emptying of the gallbladder due to the Priodax itself (2). While the search for a better medium has continued, Priodax has been widely used and with it a fairly standardized method of cholecystography has been developed, with *ante-cibum* and, one hour later, *post-cibum* films.

In 1951, Dunne *et al.* (4) and Christensen and Sosman (3) described a new medium with the trade name Telepaque, having the chemical structure 3-(3-amino-2,4,6-triiodophenyl) - 2 - ethyl - propanoic acid. Morgan and Stewart (12) and Everett and Rigler (5), in 1952, reported further studies with Telepaque, indicating that it is not only superior to Priodax but, in fact, approaches the ideal as an oral medium for gallbladder and biliary duct studies.

Telepaque is an iodine substituted organic compound. The iodine content is 66.68 per cent compared to 51.38 per cent for Priodax. The side-reactions are decreased with Telepaque in both number and severity to the point where, for all practical purposes, they can be ignored.

At the same time, the density of the x-ray shadow has been increased by at least 35 per cent over that obtained with iodoalphonic acid (12).

METHOD

With the appearance of the reports cited above, Telepaque was adopted for cholecystography in this hospital and its superior properties were confirmed. The cystic and common bile ducts were frequently demonstrated on the *post-cibum* films as reported by others (3, 5), and their visualization was surprisingly clear. The oblique film was found most reliable for showing the length of the cystic and common ducts without interference from the spine. The question naturally arose as to whether Telepaque would make it possible, using new time intervals, to visualize the biliary ducts as well as the gallbladder in all patients examined.

For a few weeks all patients scheduled for cholecystography had the routine initial films taken. Immediately following these films, the patient was given the usual fatty meal, followed by films of the gallbladder area taken at ten-minute intervals to sixty minutes. The cystic and common bile ducts were seen on approximately 60 per cent of the ten-minute films and 100 per cent of the twenty-minute films in a series of 26 cases. It was also noted that the gallbladder was shown to have emptied to its maximum degree on the majority of the forty-minute films. These findings were, of course, only for functioning gallbladders.

With this information, a standardized technic was adopted. The Telepaque was administered in the usual manner and dosage (3 grams) following the evening meal in

¹ From The Springfield Hospital, Springfield, Mass. Accepted for publication in November 1952.

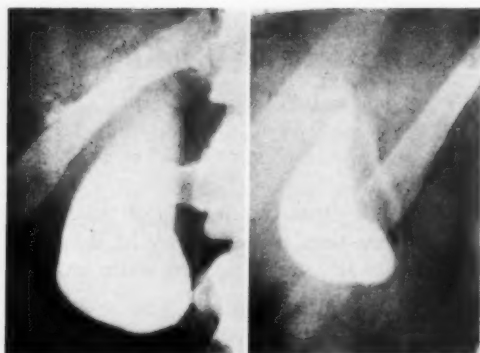


Fig. 1 The film on the left shows the dense shadow obtained with Telepaque. The *post-cibum* film, on the right, shows the same gallbladder partially emptied and demonstrates the common and cystic ducts, which are normal.

the hospital group and at 9 P.M. in the outpatient group. The patients reported to the X-ray Department between the hours of 8:00 and 9:30 the following morning. At this time a 14 × 17-inch film of the abdomen and postero-anterior and oblique 10 × 12-inch coned films of the gallbladder area were obtained. As soon as the films were checked for technic and positioning, a fatty meal consisting of an egg nog containing 2 egg yolks, 2 ounces of cream, and vanilla was given. The patient remained on the x-ray table and was encouraged to lie on his right side to facilitate emptying of the stomach. At fifteen minutes the two films of the gallbladder area were repeated and developed immediately, the fifteen-minute interval being chosen in the hope of reducing the time per examination. If the biliary ducts were not shown, a second pair of films was obtained at twenty-five minutes. In the beginning, an additional film at forty minutes was made on each patient. The technicians learned rapidly to recognize the common bile duct, so that direct supervision by the radiologist was not necessary following the first few examinations. Figure 1 shows the typical *ante-cibum* and *post-cibum* coned films.

RESULTS

With this standardized oral technic, 146 patients have been examined, with non-functioning gallbladders recorded in 14

instances. In the 132 functioning cases the cystic and common bile ducts were satisfactorily demonstrated 121 times. The method failed, therefore, in 11 examinations. In 4 of these cholelithiasis was present and in 4 the cystic duct was plainly shown. At least 2 of these 11 patients



Fig. 2. Cholesterol calculi in the gallbladder and in the dilated cystic and common ducts. The large calcification is in the liver.

were quite obese, and it may be that re-examination with a double dose of the medium should have been carried out. The hepatic duct was shown in 9 and the duodenum in 17 examinations.

This incidence of 121 demonstrations of the cystic and common bile ducts in 132 examinations (91+ per cent), enabling the radiologist to describe their patency and anatomy, warrants the adoption of this method as a new routine in gallbladder study. In the 121 satisfactory examinations, cholelithiasis was present 14 times and in 3 of these a partial obstruction of the common bile duct was demonstrated, with calculi plainly visible in the duct. In the remaining 11 cases of cholelithiasis normal cystic and common ducts were visualized. An additional case of normal gallbladder showed a partial obstruction of the common duct due to an enlarged calcified lymph node. Without visualization

of the biliary ducts, the lymph node would have been mistaken for a calculus in the common duct. One interesting examination revealed distended, tortuous cystic and common ducts without calculi, due to a small pancreatic cyst producing obstruction. All of the abnormal findings were confirmed at surgery. The choice of a fifteen-minute interval for the *post-cibum* set of films appears to be most appropriate, since only 2 patients needed to be re-examined at twenty-five minutes to demonstrate the biliary ducts following non-filling at fifteen minutes.

With this method, *post-cibum* films should always be taken, especially when cholelithiasis is demonstrated on the earlier films. Mild clinical jaundice or laboratory evidence of jaundice is not a contraindication to the procedure, which in this series has been quite valuable in three such instances. Several cases of frank jaundice were examined but, as would be expected, no function was demonstrated. No difficulty in interpretation due to the presence of Telepaque in the colon was experienced. In 3 of the cases of cholelithiasis function was not demonstrated with Priodax. In addition to the diagnostic improvements obtained by this method, surgeons have found the demonstration of the size, anatomy, and relationships of the biliary ducts helpful at the time of operation. Following these 121 cases, the forty-minute film has been omitted except where the history is strongly typical of gallbladder disease or in those patients in whom the gallbladder shadow had not decreased more than 20 per cent in size on the fifteen-minute films. By this last maneuver the overall examination time has been reduced to less than one-half hour in most examinations, which is a significant saving to both the patient and the X-ray Department compared to the usual method of taking the *post-cibum* films at one hour.

CONCLUSIONS

1. Telepaque has now proved itself a superior medium for oral cholecystography and should replace other preparations.



Fig. 3. Gallbladder containing calculi, with normal common and cystic ducts.

2. A method of oral cholecystography using Telepaque to visualize both the gallbladder and bile ducts has been described. The results (over 91 per cent visualization of the bile ducts) in a small series are excellent and have been so consistent that demonstration of the bile ducts should become an important part of oral cholecystography if these results hold for larger series of examinations. With this method, the time per examination has been reduced to thirty minutes in most instances.

3. The preoperative demonstration of the cystic, common, and at times hepatic ducts is giving new and more exact diagnoses of biliary abnormalities and is of value to the surgeon in both planning and performing the operative procedure.

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SUMARIO

Técnica Colecistográfica Oral Usando Telepaco para la Observación del Conducto Cístico y del Colédoco

El Telepaco ha resultado ser un medio superior para la colecistografía oral, produciendo un mínimo de reacciones subsidiarias y una densidad satisfactoria de la imagen radiológica. A los AA. les ha resultado útil para la observación del conducto cístico y del colédoco y describen su técnica para dicho fin. El medio se administra oralmente (3 gramos) por la noche antes del examen. Se toma una radiografía abdominal de 35 X 42.5 cm. y radiografías postero-anteriores y oblicuas en cono de la zona de la vesícula biliar. Inmediatamente después se suministra una comida grasa y se toman radiografías a los

quince minutos (repitiéndose a los veinticinco minutos si no aparecen los conductos biliares en el examen a los quince minutos). Con este procedimiento se descubrieron los conductos en 121 de 132 exámenes de vesículas biliares en funcionamiento, o sea en más de 91 por ciento. La duración del examen ha sido rebajada en la mayor parte de los casos a unos treinta minutos.

La observación preoperatoria de los conductos cístico, colédoco y a veces hepático, proporciona nuevos y más exactos diagnósticos de las anomalías biliares y es de valor al cirujano al proyectar y ejecutar el procedimiento operatorio mismo.



Gas Embolism During Extraperitoneal Insufflation

Recovery in the Left Decubitus Position¹

FRANK H. RUSS, M.D., DONALD L. GLENN, M.D., and CESARE GIANTURCO, M.D.

EXTRAPERITONEAL air insufflation done through a single presacral puncture is a simple procedure which is considered safe by those workers who have used it in large numbers of cases. Mosca (2) collected over 1,500 cases without fatal accidents. Ruiz Rivas (4), one of the originators of the method, stresses the fact that a needle inserted in the mid-line between the rectum and the sacrum encounters no large vascular channels. For this reason, gas embolism is considered unlikely. That it may occur is shown by the following case.

A woman, 74 years of age, was subjected to extraperitoneal insufflation to localize a high retroperitoneal tumor. The needle was inserted in the usual manner, aspiration was done without obtaining blood, and the insufflation was started with oxygen at a pressure of 30 cm. of water. The patient was in the left decubitus position. In about fifteen minutes, 500 c.c. of oxygen were injected without difficulty. The patient was then placed in the prone position to obtain a better distribution of the gas. After the injection of another 100 c.c. of oxygen, she suddenly became dyspneic, then cyanotic. The skin was clammy, the blood pressure was unobtainable, and the pulse irregular and thread-like at 120 beats per minute. The insufflation was discontinued. Two minims of adrenalin were administered, and, in order that the heart beats might be followed, the patient was rolled over on her back. A loud "millwheel" sound could be heard with each beat, unmistakable evidence of gas in the heart.

The patient had become very restless and anxious and resented the oxygen mask. Her distress was especially marked in the supine position. At this point, she was again turned on her left side. In a few minutes the "millwheel" sound disappeared and she became slightly more comfortable. The pulse rate was now 160. Cyanosis and apprehension continued for approximately thirty minutes. Gradually the pulse rate dropped to 104 per minute, the color became normal, and the patient relaxed. At no time was she unconscious. In fact, she recalled vividly the "suffocating sensations," which were extreme in the prone and supine positions.

About three hours later a film of the abdomen revealed no gas in the extraperitoneal spaces.

The absence of gas in the extraperitoneal spaces after three hours is significant. Since oxygen is not reabsorbed in so short a time, one must postulate that the majority, if not all, of the 600 c.c. was injected directly into the venous system. The survival of the patient in spite of the intravenous injection of such a quantity of gas may be explained by the experimental work of Durant, Long, and Oppenheimer (1).

These authors, working with dogs, found that with a slow rate of injection the animals could tolerate large amounts of intravenous gas. When gas was injected fairly rapidly, fatal embolism developed when the dogs were kept on the right side, on the back, or in the prone position. The tolerance was greatly increased if the left decubitus position was maintained during the injection. In this position gas does not accumulate in the right ventricle but is whipped into a froth and propelled in the pulmonary circulation, where it is eliminated. Durant, Long, and Oppenheimer also noted that animals in which the injection was done in the supine, prone, or right-sided positions, and in which right ventricular failure was already evident, recovered promptly when placed in left decubitus. In the light of this experimental work, our case may be interpreted as follows:

- (1) The slow intravenous injection of the first 500 c.c. of oxygen, while the patient was on the left side, was well tolerated.
- (2) The subsequent injection of 100 c.c. of oxygen caused right ventricular embarrassment because the patient was in the prone position. In this position the oxygen formed an "air lock."

¹ From the Departments of Surgery (F.H.R.), Internal Medicine (D.L.G.), and Radiology (C.G.), Carle Memorial Hospital and Carle Hospital Clinic, Urbana, Ill. Accepted for publication in October 1952.

- (3) Recovery followed the return to the left-sided position.

This interpretation is substantiated by the recent observation of Musgrove and MacQuigg (3), who reported a case of gas embolism during pneumoperitoneum in which recovery followed the assumption of the left decubitus.

In view of the evidence presented above, it seems that the catastrophic effects of gas embolism may be avoided or minimized by using a slow rate of injection, by maintaining the gas at low pressure, and by keeping the patient in the left decubitus during the injection and for some time thereafter.

It should be stressed that no insuffla-

tion is completely safe and that gas may enter the venous system even when the injection is done in the relatively avascular tissues of the presacral space.

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SUMARIO

Embolia Gaseosa Durante la Insuflación Extraperitoneal; Curación en Decúbito Izquierdo

Preséntase un caso de embolia gaseosa que ocurrió mientras se ejecutaba una insuflación de aire para diagnóstico. La insuflación comenzó con el enfermo en posición de decúbito izquierdo, introduciéndose 500 c.c. de oxígeno a una presión de 30 cm. de agua, sin efecto adverso. Luego se colocó al sujeto en decúbito prono para obtener mejor distribución del gas, y se introdujeron otros 100 c.c. De repente aparecieron síntomas de intenso malestar con disnea y cianosis, y signos inconfundibles de gas en el corazón. El malestar se acentuaba en particular en la posición

supina, pero el retorno al primitivo decúbito izquierdo fué seguido de restablecimiento.

A las tres horas del incidente, las radiografías abdominales revelaron falta absoluta del gas en los espacios extraperitoneales, indicando que la mayor parte del oxígeno, sino todo, había sido inyectado directamente en el sistema venoso. La reposición del enfermo se considera debida a que, en decúbito izquierdo, el gas no se acumula en el ventrículo derecho, sino que es batido a espuma e impulsado a la circulación pulmonar, por la cual se expulsa.



Basilar Impression and Platybasia in Paget's Disease¹

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BASILAR impression (known also as basilar invagination) and platybasia are not synonymous nor need they necessarily be coexistent simultaneously or otherwise. Their only relationship lies in the fact that both represent specific types of abnormality of shape of a portion or portions of the base of the skull which under certain conditions may coexist. Basilar impression is related to the entire foramen magnum region of the floor of the posterior fossa, while platybasia is related to the floors of the anterior and middle cranial fossae and involves only that portion of the floor of the posterior cranial fossa which extends from the dorsum sellae to the anterior margin of the foramen magnum.

Accordingly, basilar impression may be defined as an abnormal cephalad invagination of the foramen magnum region as determined by the relation of the odontoid process to Chamberlain's line (1), which is drawn from the posterior margin of the hard palate to the posterior margin of the foramen magnum on the lateral roentgenogram (Figs. 1 and 2). (McGregor (2) draws a line from the posterior margin of the hard palate to the lowermost point of the occipital bone.) If the odontoid process is significantly above Chamberlain's line, basilar impression is present. In addition, a frontal view (3) may show asymmetry of the posterior cranial fossa and foramen magnum; upward displacement of the atlas as well as the axis; an abnormal relationship of the atlas and odontoid process to the lumen of the foramen magnum; abnormality of the atlanto-occipital articulations; an unusual shape and asymmetry of the petrous portions of the temporal bones, and a broadened biparietal measurement (basionic diameter). The lateral view (3) may reveal a rudimentary development of

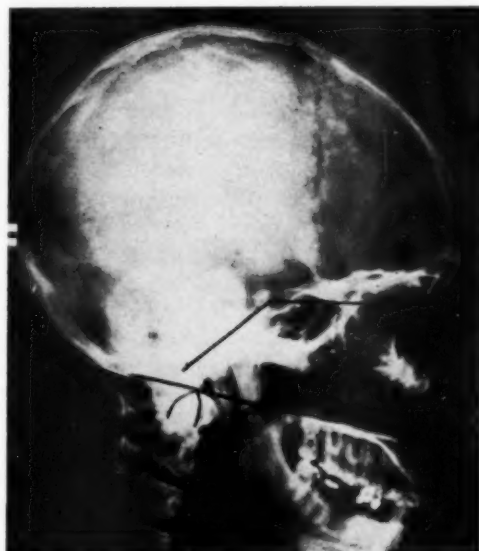


Fig. 1. Normal skull showing basal angle, Chamberlain's line, and odontoid process.

the occipito-atlanto-axial region; upward and forward dislocation of the atlas and axis; upward displacement of the clivus; invagination of the posterior rim of the foramen magnum; high position of the petrous portions of the temporal bones, and a relatively long and vertically narrow appearance of the cranial cavity.

While one or more of these abnormalities may be noted in any one case, their existence is not reliably constant in all cases, so that the only accurate index is a significant projection of the odontoid process above Chamberlain's (or McGregor's) line.

Platybasia is an abnormal obtuseness of the relationship of two specific segments of the cranial floor. The first segment is represented by a line (Figs. 1 and 2) which extends from the nasion to the center of the sella turcica, and the second segment by a line extending from the latter point to the

¹ From the Departments of Radiology, Veterans Administration Hospital, Bronx, N. Y., and New York University Post-Graduate Medical School. Accepted for publication in October 1952.

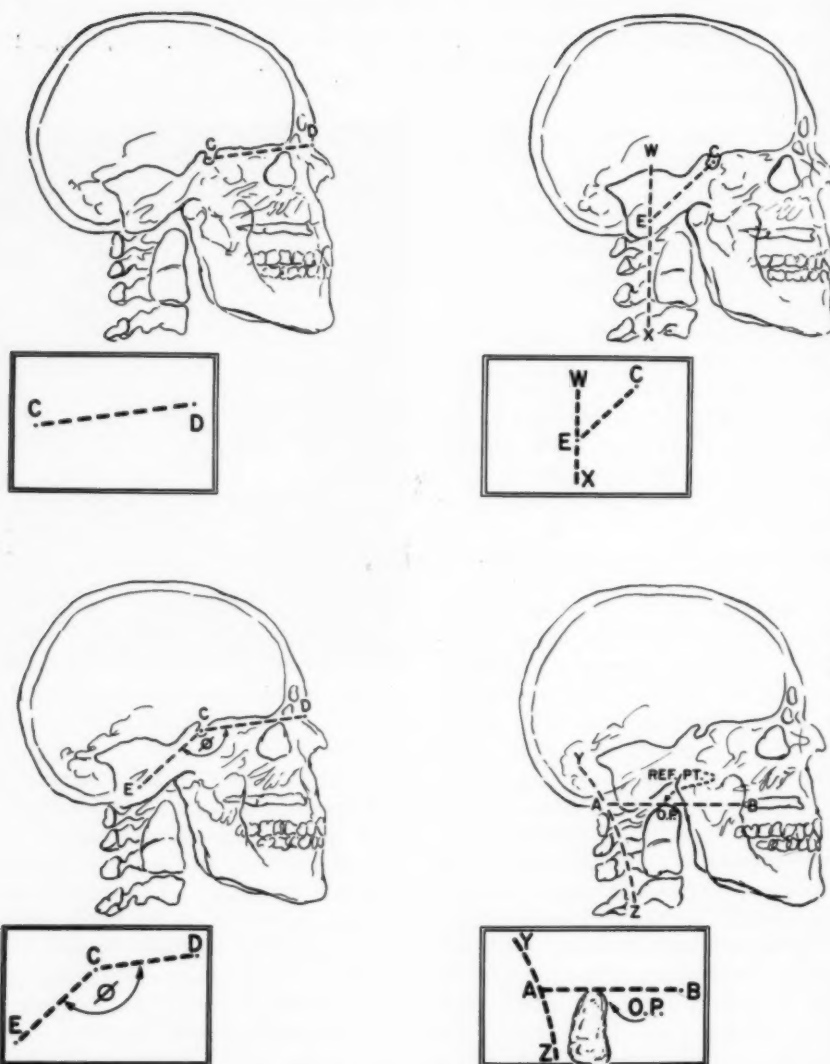


Fig. 2. Determination of the basal angle and Chamberlain's line.
 O.P. Upper tip of odontoid process
 A. Junction of posterior border of spinal canal with base of skull, which for practical purposes is considered the posterior margin of the foramen magnum
 B. Posterior tip of hard palate
 C. Center of sella turcica
 D. Nasion
 E. Junction of the anterior border of the spinal canal with the anterior margin of the foramen magnum
 A-B. Chamberlain's line
 W-X. Line indicating anterior spinal canal border
 Y-Z. Line indicating posterior spinal canal border
 ϕ . Basal angle
 Ref. Pt. Relation of odontoid process to Chamberlain's line

anterior margin of the foramen magnum on the lateral roentgenogram. The inferior angle subtended by these two lines is termed the basal or sphenoid angle. This angle represents the fundamental shape of the base of the skull only as far posterior as the anterior margin of the foramen magnum. The region of the foramen magnum itself is posterior to the above segments and is excluded from the angle determination. An abnormality in shape of the foramen magnum region, therefore, will not be represented in the basal angle unless the deformation involves the position of the anterior margin. Parenthetically, an abnormal smallness of the basal angle is termed basal kyphosis.

Table I shows the measurements of the basal angle in a series of normal skulls ex-

TABLE I: NORMAL RANGE OF BASAL ANGLE
(To the nearest unit)

	Mean	Maximum	Minimum
Brailsford's series	135°	149°	121°
McGregor's series (Bantu)	134°	148°	121°
Present normal series	137°	152°	123°

amined by Brailsford (4) and a series of 203 Bantu skulls, also normal, studied by McGregor. The table includes also a summary of the measurements of the basal angle obtained by us in 102 normal cases. It is seen that normally the basal angle ranges from 121 to 152°, with a composite mean between 134 and 137°.

According to Gvozdanović and Dogan (5), the earliest descriptions of basilar impression were those of Ackerman (1790), Rokitsky (1846), Berg and Retzius (1855), Boogard (1865), and Virchow (1876), who first used the term platybasia. The first radiological description was by Schüller (6), who pointed out that the most striking feature of basilar invagination is the upward bulging of the floor of the posterior cranial fossa about the foramen magnum. Chamberlain described the line that bears his name but failed to differentiate between platybasia and basilar impression.

Basilar impression is of two types: primary (congenital) and secondary (acquired). The congenital type is apparently the most common (5) and is due to maldevelopment of the basiocciput, atlas, and axis. The acquired type results from generalized osteoporotic conditions (such as osteomalacia, rickets, senile atrophy, hyperparathyroidism, Paget's disease), delayed or defective ossification of the cranial bones (such as osteogenesis imperfecta, osteochondrodystrophy, cretinism, cranioleiodysostosis), localized bone destruction, and trauma (2).

We are concerned in this presentation only with basilar impression and platybasia in Paget's disease but have included the above as a frame of reference for our discussion in relation to the entire subject.

The clinical manifestations of basilar impression may resemble Arnold-Chiari syndrome, syringomyelia, amyotrophic lateral sclerosis, cerebellar or high cervical tumors, or any syndrome or entity responsible for upper cervical cord compression.

Paget's disease is a deforming osteosis of unknown origin. It frequently involves the bones of the skull, manifesting itself either as an area of osteoporosis circumscripta or as a localized or diffuse thickening of the diploic structures with interspersed zones of radiolucent defects and condensation. A review of the literature revealed reports of 13 cases of Paget's disease of the skull with basilar impression (3, 7, 8, 9, 10).

We have collected a series of 75 cases of Paget's disease with involvement of the skull demonstrable roentgenologically. Twelve of these cases show osteoporosis circumscripta as the only skull manifestation. The remaining 63 cases show the characteristic findings in varying degree from the slight and localized forms to the extreme and diffuse forms. The basal angle could be determined in 71 of the 75 cases and Chamberlain's line in all.

Along with this work on Paget's disease, we collected 102 unselected normal consecutive skulls (predominantly male), in



Fig. 3. Paget's disease showing basilar impression.

each of which the basal angle and the relationship of the odontoid process to Chamberlain's line were determined.

In the 102 normal skulls the mean of the distance between the tip of the odontoid process and Chamberlain's line was essentially 0 (actually $+0.06$ mm.). For this series the standard deviation was 3.3 mm., and the standard error of the mean was 1.1 mm. A plus sign indicates that the top of the odontoid process is above Chamberlain's line and a minus sign indicates that it is below.

TABLE II: COMPARISON OF RELATIONSHIP OF ODONTOID PROCESS TO BASE LINE IN THREE SERIES OF NORMAL SKULLS

	Number of Cases	Mean Position of Tip of Odontoid Process in Relation to Chamberlain's Line (mm.)	Standard Deviation (mm.)
Saunders	100	-1	± 3.6
McGregor* (Bantu)	203	-1.32	± 2.62
Present series	102	$+0.06$	± 3.3

* McGregor used a base line drawn from the posterior hard palate to the lowest point of the occiput. He used a plus quantity if odontoid process was below the base line and a minus quantity if it was above. The sign of these quantities has been reversed here so that his series can be compared with the other two.

Our series is compared in Table II with a series of 100 skulls measured by Saunders (11) and the 203 Bantu skulls measured by McGregor.

In our 75 cases of Paget's disease similar measurements were obtained and evaluated statistically. Here, the mean distance between the odontoid process and Chamberlain's line was $+5.2$ mm. The standard deviation was 3.8 mm. and the standard error of the mean was 1.2 mm. These values are summarized in Table III.

TABLE III: STATISTICAL ANALYSIS OF RELATIONSHIP OF THE ODONTOID PROCESS TO CHAMBERLAIN'S LINE IN 102 NORMAL SKULLS AND IN 75 CASES OF PAGET'S DISEASE

	Normal (mm.)	Paget's Disease (mm.)
Mean	0.06	5.2
Standard deviation	± 3.3	± 3.8
Standard error	± 1.1	± 1.2

The difference between the means for the normal series and the Paget's disease series is 4.7 times the standard error of the mean for the normal series. This indicates a significant tendency toward basilar impression in the cases of Paget's disease.

In evaluating individual measurements, it is necessary to establish a statistically significant variation from the mean in order to determine the presence of basilar impression. According to accepted statistical data, the range between $+2$ and -2 standard deviations from the mean should include 95.4 per cent of all normal cases; 4.55 per cent should be beyond this range. In our normal series 2 standard deviations from the mean is 6.6 mm. Four of the 102 normal cases or 4.0 per cent were beyond this limit. As this compares favorably with the expected 4.55 per cent, the series is considered representative. Since we are interested only in the position of the odontoid process above Chamberlain's line (plus values), the percentage of normals beyond 2 standard deviations from the mean should be one-half of 4.55 or 2.27 per cent. In our normal series, 2 cases or 1.96 per cent were 2 standard deviations above Chamberlain's line. Therefore, in any individual case, 2 standard deviations (6.6 mm.) or more above the mean for the normal series may be considered strongly indicative of basilar impression.

Of our 75 cases of Paget's disease, 27 (36 per cent) showed the odontoid process more than 6.6 mm. above the normal mean position.

In the 102 normal cases the basal angle was also measured. The mean basal angle for this series is 136.7° , with variations from 123 to 152° . The standard error is 5.2° . The mean basal angle for the Paget's series is 132.6° , with a variation of actual measurements from 110 to 149° . The mean basal angle of the Paget's disease series is thus 4.1° less than that of the normal series. This is within the standard error of the normal series and therefore is of no statistical significance. Thus there is no significant trend toward platybasia in our series of Paget's disease cases. McGregor similarly found no relationship between basilar impression and the basal angle in the African Bantu.

In carrying out our measurements, we were impressed with the idea of using lateral midline laminagraphy (5) in cases of Paget's disease of the skull. This is particularly necessary where the odontoid process is not distinctly outlined (Fig. 4).

Routine evaluation of skull roentgenograms in all cases of Paget's disease is of more than academic interest. Mild, bizarre, unexplained symptoms and/or signs referable to varying degrees of cord compression may be brought into sharp focus for the clinician by the demonstration of basilar impression. Surgical intervention may then be life-saving. A permanent record of Chamberlain's line-odontoid process relationship is important in following cases of Paget's disease with skull involvement. Changes in these factors occurring in the wake of signs of cord compression will lead to a correct evaluation of the situation. We feel, therefore, that the Chamberlain's line-odontoid process relationship should be made a permanent part of the official interpretation of every case of Paget's disease with or without demonstrable skull involvement. This principle could very well be applied to any malacic or softening disease of the skull bones.

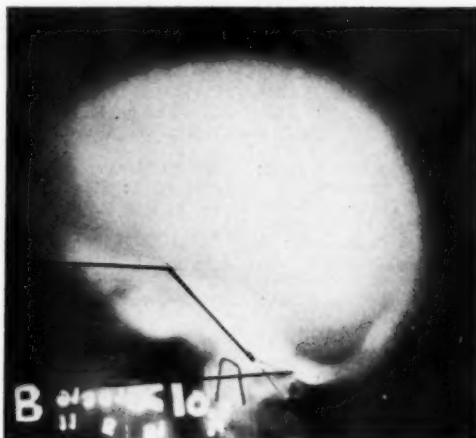


Fig. 4. Paget's disease showing basal measurements on sagittal laminagraph. Note basilar impression.

CONCLUSIONS

1. There is a fundamental and significant difference between basilar impression and platybasia in that the two conditions are primarily concerned with different areas of the base of the skull.
2. There is a statistically significant trend toward basilar impression in Paget's disease involving the skull. In our series of 75 cases, basilar impression occurred 27 times, *i.e.*, in 36 per cent of the cases. This percentage would probably be increased by re-examination at a later date, when the disease has become more advanced.
3. The incidence of platybasia in our series of Paget's disease of the skull is not significant.
4. Basilar measurements should be a standard and routine part of every roentgenologic study of the skull. This should apply to instances where the skull is obviously involved as well as to those cases in which it is not yet invaded by a known Paget's disease.
5. A plea for the use of lateral midline skull laminagraphy is entered.

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SUMARIO

La Impresión Basilar y la Platibasia en la Enfermedad de Paget

Existe una diferencia fundamental entre la impresión basilar y la platibasia, por afectar primariamente esos dos estados distintas zonas de la base del cráneo. La impresión basilar guarda relación con toda la región del agujero magno en el suelo de la fosa posterior, mientras que la platibasia interesa los pisos de las fosas craneales anterior y media y, en la fosa posterior, sólo afecta la parte que va desde el dorso de la silla turca hasta el borde anterior del agujero occipital.

En la enfermedad de Paget, cuando ataca el cráneo, nótase una tendencia de importancia estadística hacia la impresión basilar. En una serie de 75 casos de dicha dolencia con invasión craneal observable roentgenológicamente, se descubrió impresión basilar

27 veces (36 por ciento), y parece que exámenes subsiguientes, cuando la enfermedad esté más avanzada, revelarían una incidencia todavía mayor. La incidencia de platibasia en la serie fué insignificante.

Las mediciones basilares deberían formar parte constante de todo examen roentgenológico del cráneo, lo cual reza tanto en casos en los que el último está manifiestamente atacado como con aquéllos en los que no ha sido todavía invadido por una enfermedad de Paget reconocida.

A los AA. les ha resultado de mucho valor la laminagrafía mesolineal lateral en casos de enfermedad de Paget del cráneo, sobre todo en aquéllos en que no se halla netamente demarcada la apófisis odontoides.



Failure in Modeling of Bone¹

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THE PROCESS OF bone growth is influenced by two main and complementary factors: first, the regulation of longitudinal growth by the metaphyseal cartilage, and second, the shaping of bone by the periosteum. These two factors are synchronized in their action, in that the new bone created at the metaphyseal cartilage is molded into its predestined shape by periosteal osteoclastic and osteoblastic activity. This synchronized action was designated by Hunter "modeling of the bone." The new bone is formed with a waist-like "constriction" above the metaphysis and not as a direct continuation of the old bone.

The "double contour" seen in roentgenograms of the long bones of infants in the first months of life, regarded by Glaser as the "effect of crests of bone," is in my opinion to be attributed to periosteal activity, in the sense of normal modeling.

This modeling process, which conserves the tubular form at the metaphysis, can be observed by superimposing roentgenograms of a limb of an infant obtained at different ages. Thus we can follow the modeling of the newly created bone within the limits of the old metaphysis, in the form of a *waist-like "constriction"* (Fig. 1A). When this normal process of modeling is disturbed, the bone continues its growth in a straight line and is broadened in a club-like form at the metaphysis, losing the tubular shape of normal bone (Fig. 1B).

This failure in modeling manifested as "underconstriction," or under-tubulation, is present in several diseases of bone in which the normal coordination of cartilaginous growth and periosteal bone shaping is interrupted. The club-like metaphyseal swelling of Gaucher's disease and Cooley's anemia, for example, is well known. This metaphyseal broadening is

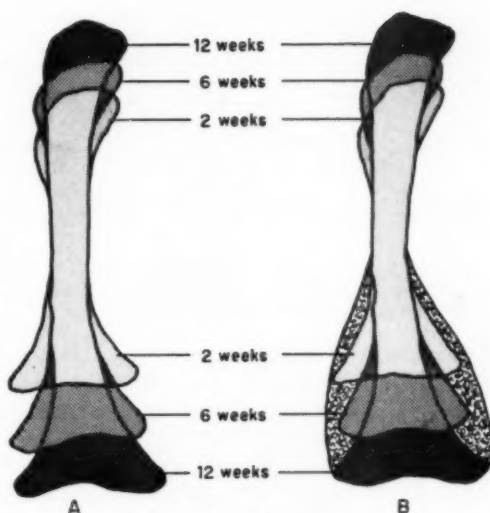


Fig. 1. A. Normal modeling. The newly created bone is seen within the limits of the old metaphysis in the form of a waist-like constriction. B. Failure of modeling, resulting in a club-like deformity at the metaphysis.

caused not by augmented intramedullary pressure, as was once thought—and expressed by the word "swelling"—but, rather, I believe, by a failure in the normal function of the periosteum.

Bone transformation, being a slow and gradual process, does not lend itself easily to exact radiological observation. We were able, however, in a child of nine with Cooley's anemia of several years duration, to observe the presence of new bone formation, apparent as thin calcified parosseal deposits near the femoral metaphysis (Fig. 2A) while at the same time the breakdown of bone was demonstrable in the form of cortical defects at the distal end of the tibia (Fig. 2B).

The abnormal modeling of bone in Cooley's anemia is presented graphically in a diagram comparing the roentgenograms

¹ From the X-ray Department of the Municipal Hospital Hadassa, Tel Aviv, Israel. Accepted for publication in October 1952.



Fig. 2. Bone transformation in Cooley's anemia. A. New bone formation at distal end of femur in the form of para-osseal deposits. B. Breakdown of bone at distal end of tibia manifest as cortical defects.

over a period of six months. In this way the metaphyseal broadening caused by the absence of the normal rate of constriction can be demonstrated (Fig. 3).

Disturbance of normal calcification of the metaphyseal cartilage in rickets also

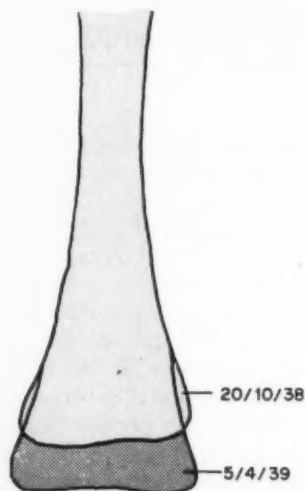


Fig. 3. Failure of modeling in Cooley's anemia. Metaphyseal broadening caused by absence of the normal rate of constriction.

causes a metaphyseal broadening which may be due to "under-tubulation" or to "underconstriction." A similar deformity occurs in osteomyelitis and appears mainly in that stage of the disease, when resorption of the sequestra is beginning, the

stage which we prefer to call the third stage, when longitudinal growth is preserved and the sequestra are pushed from the metaphysis into the diaphysis. The sequestrum is a source of irritation and leads to a disturbance of the normal physiology and a change in modeling of the

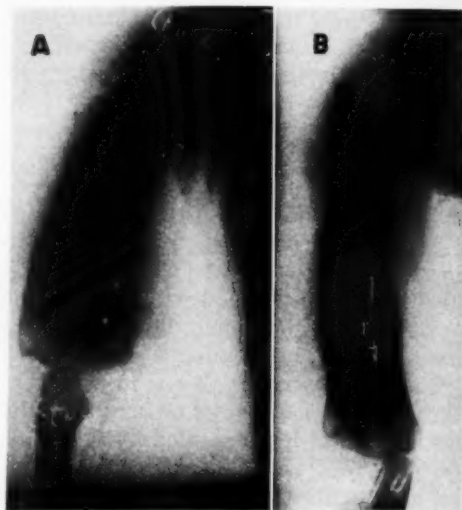


Fig. 4. Failure in modeling and remodeling in osteomyelitis. A. Stage 3: Sequestral resorption causing undertubulation. B. Stage 4: Following sequestrotomy. Retubulation indicates complete healing.

bone. This "undertubulation," which in the pre-antibiotic area was seen two or three months after the beginning of the infection, can be considered as a sign that resorption of the sequestra is taking place. After resorption has been completed, or after sequestrotomy, the bone begins to regain its normal shape. This "retubulation" is a certain sign of complete healing in osteomyelitis (Figs. 4 and 5).

In some pathological conditions the periosteal cuff does not increase in length at the same rate as the metaphyseal bone, and a lack of periosteal covering occurs at the metaphysis. In these cases the bone develops from the cartilage and is broadened laterally. The dissociation in longitudinal growth of bone and the length of the periosteum has been considered by Keith as the underlying cause of multiple exostoses and is probably the cause of undertubulation.

The explanation of broadening of the bone through failure in the normal function of the periosteum has recently been confirmed by Weiss in a paper on the pathogenesis of osteitis deformans (Paget's disease). In his opinion the theory that the bone is thickened by central swelling and pressure is untenable. He maintains that, wherever thickening of the bone occurs, it must be as a result of periosteal deposition.

CONCLUSION

The pathological broadening of bone at the metaphysis is not pathognomonic of any one disease, as is widely recognized, but is the expression of a pathobiological process leading to a disturbance in the coordination of growth by metaphysis and periosteum. This failure in the normal physiological conditions of modeling may be produced by quite different mechanisms. Thus we may explain the fact that in such different pathological entities as Gaucher's disease, Cooley's anemia, osteomyelitis, and rickets the same deformities of bone are observed.

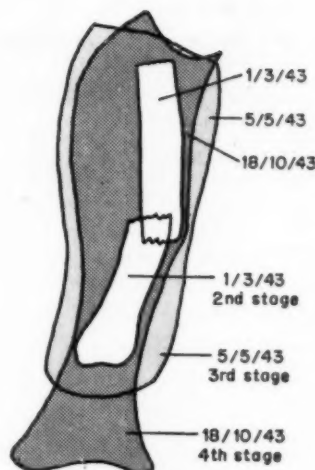


Fig. 5. Diagrammatic representation of the course of osteomyelitis (femur). Stage 2: Pseudo-healing two weeks after infection. Sequestration and pathological fracture. Stage 3: Two months later. Sequestral resorption; thickening of bone; undertubulation. Stage 4: Five months later, post-sequestrectomy. Retubulation indicative of healing.

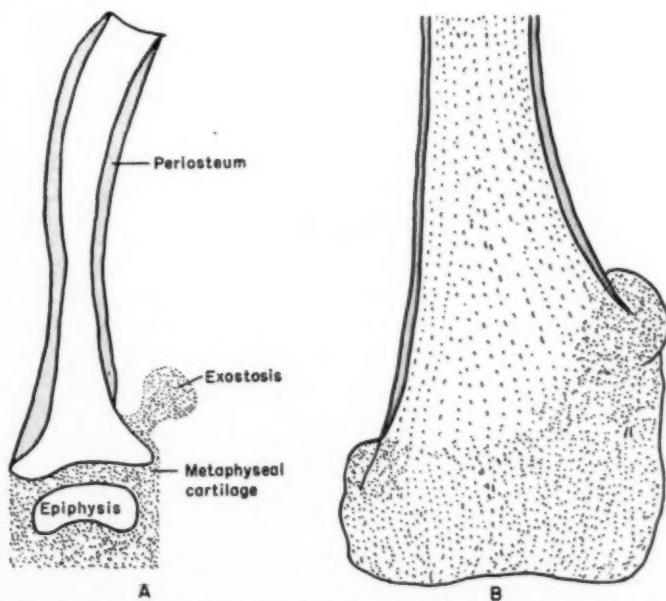


Fig. 6. A. Genesis of exostoses (according to Keith). B. Dissociation in longitudinal growth and length of periosteum (periosteal shortening). Failure in modeling in multiple exostoses as observed in a twelve-year-old male. Undertubulation.

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SUMARIO

Falta de Moldeamiento del Hueso

La sincrónica creación de hueso nuevo en el cartilago metafisario y su moldeamiento en la forma correspondiente por medio de la actividad osteoclástica y osteoblástica del periostio ha sido denominada "modelado del hueso." Al trastornarse ese proceso normal de modelado, tiene lugar un ensanche patológico de la metafisis,

que puede observarse en la radiografía. Ese fenómeno no es patognomónico de ninguna enfermedad dada ni tampoco producido por un solo mecanismo, hallándose presente en entidades patológicas tan distintas como son la enfermedad de Gaucher, la anemia de Cooley, el raquitismo y la osteomielitis.



EDITORIAL

Renal Damage in X-Ray Therapy

Despite considerable evidence to the contrary, there is widespread belief that renal tissue is relatively resistant to radiation. As the adoption of British methods of x-ray therapy becomes more widespread, with consequent use of large abdominal fields, particularly in cases of seminoma testis and certain ovarian lesions, it seems appropriate to emphasize the danger of overdosage to the kidneys.

In 1926 and 1927, Doub, Hartman, and Bolliger published a number of articles dealing with the effects of radiation on the renal tissue of dogs. They showed that, contrary to what was then established opinion, renal tissue was quite sensitive to radiation and that in dogs nephritis could be produced with doses so low that epilation did not occur. They noted various phases of nephritis in their animals, ranging from acute to chronic kidney disease. The chronic stage described by them is of particular interest in view of the similarity to human disease. The most pronounced change occurred in the tubules. In some large areas of cortex, tubules were absent; in other areas, those remaining were distorted. The glomeruli, on the whole, were relatively well preserved. Clinically, these animals showed signs of nitrogen retention and lowered urinary output, albuminuria, hypertension, retinopathy, edema, and acidosis. In a later article, the same authors reported two cases of their own and referred to 16 cases of others, in which clinical nephritis developed following radiation therapy to the kidney area.

The published statistics of the Christie Hospital leave little doubt as to the value of prophylactic irradiation in seminoma testis, but a recent article by Paterson

and another by his colleagues, Kunkler, Farr, and Luxton, emphasize the great danger of kidney damage when both kidneys receive a dose exceeding 2,300 r in five weeks or less. With the characteristic thoroughness of the Manchester group, observations on 93 patients treated for seminoma were carefully analyzed as to dose and method of treatment. Twenty-two patients were found to have suffered renal damage. All of these fell in a group where higher doses had been used, beam flattening filters were employed, and treatment was given over large fields. Seven of these patients died. It is pointed out that in some of the earlier technics much larger doses were given to portions of the kidneys, while lower doses were received by other renal areas. The authors also emphasize the lack of effect of high integral dose. They ascribe the renal failure seen by them to direct damage to all the renal tissue and point out that their technics which did not produce renal failure gave a low dose to the upper pole of one or both kidneys.

The clinical picture is important. The latent period ranged from six to twelve months from the start of therapy. Initially the patients complained of dyspnea, headache, ankle edema, and lassitude. They appeared pale and anemic, and hypertension was always present at some time. Anemia was refractory, and albuminuria a constant finding. There were a number of patients who remained symptom-free but who had hypertension, impaired kidney function, and albuminuria. The only successful treatment was repeated transfusion.

Paterson and his co-workers draw several important conclusions from their study of

these cases. They are convinced that where 2,300 r or more are delivered to both kidneys uniformly in five weeks, hypertension and nephritis may develop, and that such a dose is probable where an attempt is made to give 3,000 r throughout the abdomen. When one-third of the kidney volume is outside the field of radiation or is given a much lower dose than 2,300 r, the danger is considerably reduced. Lastly, emphasis is placed on the need for careful study of renal function and accurate localization of the kidneys before such treatment is undertaken. The dangers of these methods in the presence of ectopic or solitary functioning kidneys cannot be stressed too greatly.

This is another illustration of excellent research becoming lost in the literature.

Paterson candidly admits that he was not aware of the work of Doub and his associates and implies that, had he known of it, his approach would have been more cautious. J. W. J. CARPENDER, M.D.

REFERENCES

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- DOUB, H. P., BOLLIGER, A., AND HARTMAN, F. W.: The Relative Sensitivity of the Kidney to Irradiation. *Radiology* **8**: 142-148, February 1927.
- PATERSON, R.: Renal Damage from Radiation During Treatment of Seminoma Testis. *J. Fac. Radiologists* **3**: 270-274, April 1952.
- KUNKLER, P. B., FARR, R. F., AND LUXTON, R. W.: The Limit of Renal Tolerance to X-Rays. An Investigation into Renal Damage Occurring Following the Treatment of Tumours of the Testis by Abdominal Baths. *Brit. J. Radiol.* **25**: 190-201, April 1952.



RADIOLOGICAL SOCIETY OF NORTH AMERICA

THIRTY-NINTH ANNUAL MEETING

Palmer House, Chicago, Ill., December 13-18, 1953

PRELIMINARY PROGRAM

Monday, December 14

OPENING SESSION: 10:30 A.M.-12:30 P.M.

SECTION A

Call to Order. IRA H. LOCKWOOD, M.D., President
Welcoming Remarks. W. C. BORNEMEIER, M.D.,
President, Chicago Medical Society
Presidential Address. IRA H. LOCKWOOD, M.D.
The Doctor and His Heart. FRED W. FITZ, M.D.
Some Pulmonary Changes Associated With Intracardiac
Septal Defects in Infancy. KENNETH L. KRABBE-
HOFF, M.D., AND WILLIAM A. EVANS, JR., M.D.
The Significance of Variations of the Cardiac Circula-
tion Time From Angiocardiographic Studies. MEL-
VIN M. FIGLEY, M.D.
Congenital Absence of a Pulmonary Artery: Its
Demonstration by Roentgenography. STANLEY M.
WYMAN, M.D.

SECTION B: 11:00 A.M.-12:30 P.M.

Biophysical and Clinical Studies With Radiogold Seeds.
ULRICH K. HENSCHKE, M.D., AND WILLIAM G.
MYERS, M.D.
Studies on Intra-cavitary Administration of Chromic
Phosphate Containing P³². SAMUEL W. ROOT, M.D.,
MALCOLM P. TYOR, M.D., GOULD A. ANDREWS, M.D.,
AND RALPH M. KNISELEY, M.D.
Comparison of the Tracer Dose and the Therapeutic
Dose of I¹³¹ as to Thyroid Uptake, Effective Half-
Life and Roentgen Dosage. LINDON SEED, M.D.

AFTERNOON SESSION: 2:00 P.M.-4:30 P.M.

Supervoltage Diagnostic Roentgenology. WILLIAM J.
TUDDENHAM, M.D., JOHN HALE, M.S., JOHN F.
GIBBONS, M.D., AND EUGENE P. PENDERGRASS, M.D.
Radiologist's Role in Pulmonary Resection. C. C.
BIRKELO, M.D.
Chest Survey (to cover three periods). L. H. GARLAND,
M.D., Moderator
The Value of Chest Surveys from the Standpoint of
the Internist. GILBERT H. MARQUARDT, M.D.
The Radiologist and Chest Surveys. T. J. WACHOW-
SKI, M.D.
The Administrator Looks at Chest Surveys. RAY
E. BROWN
Chest Surveys as Used by the Chest Physician.
EDWIN R. LEVINE, M.D.
What the Public Thinks of Chest Surveys. ROBIN
BUERKI, M.D.

Tuesday, December 15

SECTION A: 10:30 A.M.-12:30 P.M.

Calcification of the Nucleus Pulposus in Childhood.
FREDERIC N. SILVERMAN, M.D.
Kerosene Poisoning in Infants and Children. JOSEPH
C. FOLEY, M.D., A. BRADLEY SOULE, JR., M.D.,
NICHOLAS B. DREYER, M.R.C.S., L.R.C.P., AND
EPHRAIM WOLL, M.D.
Duodenal Obstruction Due to Annular Pancreas, with
a Differential Diagnosis of Other Congenital Lesions
Producing Duodenal Obstruction. JOHN W. HOPE,
M.D., AND JOHN FRANCIS GIBBONS, M.D.
Bleeding Lesions of the Intestinal Tract in Infants and
Children. JOHN R. HODGSON, M.D., AND R. L. J.
KENNEDY, M.D.

SECTION B: 10:30 A.M.-12:30 P.M.

Effects of Irradiating Various Parts of Dividing Cells.
RAYMOND E. ZIRKLE, PH.D., AND WILLIAM BLOOM,
M.D.
Reproducibility of the Lethal Effect of Total Body
Irradiation in Mice. FRIEDRICH ELLINGER, M.D.,
AND J. E. MORGAN, Cmdr., MSC, USN
Experimental Studies on Recovery from Radiation
Injury. LEON O. JACOBSON, M.D.
Late Effects of Ionizing Irradiations. JACOB FURTH,
M.D.

AFTERNOON SESSION: 2:00 P.M.-4:30 P.M.

Roentgenological Findings in Certain Specific Condi-
tions that are Presented as Dermatological Problems.
ANDRÉ BRUWER, M.D., AND ROBERT R. KIERLAND,
M.D.
Importance of Transmarginal Radiation in Split Portal
Technic in Conventional Therapy. GERHART S.
SCHWARZ, M.D., AND A. REHAI ISLAM, M.D.
A Topographic Approach to the Roentgenological and
Pathological Examination of Laryngopharyngeal
Tumors. GILBERT H. FLETCHER, M.D., GEORGE S.
LOQUVAM, M.D., AND JACOB W. OLD, M.D.
Radiation Therapy of Pancreatitis. C. H. HEACOCK,
M.D., AND D. J. CARA, M.D.
Radiation Hazards in the Practice of Radiology.
CHARLES M. BARRETT, M.D.

THE CARMAN LECTURE: 8:00 P.M.
Observations in Atomic Medicine
Roger A. Harvey, M.D.

Wednesday, December 16**SECTION A: 10:00 A.M.-12:30 P.M.**

- A Combination Film Changer for Rapid or Conventional Radiography. LEO G. RIGLER, M.D., AND JOHN C. WATSON, R. T.
- Traumatic Rupture of the Kidney. M. R. HALL, M.D.
- Roentgenological Changes of the Bones of the Extremities After Freezing. RICHARD SCHATZKI, M.D., AND COL. HAROLD VINSON, M.C.
- Venous Aneurysms of the Mediastinum. TED F. LEIGH, M.D., OSLER A. ABBOTT, M.D., JAMES V. ROGERS, JR., M.D., AND BRIT B. GAY, JR., M.D.
- Angiography in the Evaluation of Intracranial Trauma. J. E. LOFSTROM, M.D., AND J. E. WEBSTER, M.D.

SECTION B: 10:30 A.M.-12:30 P.M.

- Effective Lateral Range of Secondary Electrons in a Free Air Chamber. F. H. ATTIX, A.B., H. O. WYCKOFF, Ph.D., AND L. DE LA VERGNE, M.S.
- Ionization of Air by Beta Rays from Point Sources. R. K. CLARK, Ph.D., S. S. BRAR, M. S., AND L. D. MARINELLI, M.A.
- Gamma Ray Absorption in Tissues and Tissue-Like Material. MARSHALL BRUCER, M.D.
- A Device for the Measurement of Tissue Dose as a Function of Specific Ionization. H. H. ROSSI, Ph.D.

AFTERNOON SESSION: 2:00-4:00 P.M.

- Improved Control of Inoperable Oral Cancer with Massive Roentgen Therapy. GEORGE WHITE, M.D., WILLIAM R. CHRISTENSEN, M.D., AND JAMES SIENIEWICZ, M.D.
- The Value of Radiation Therapy in the Management of Intrinsic Tumors of the Spinal Cord. ERNEST H. WOOD, M.D., ALFRED E. BERNE, M.D., AND JUAN M. TAVERAS, M.D.
- Irradiation Therapy in Hodgkin's Disease. CHARLES NICE, M.D., AND K. WILHELM STENSTROM, Ph.D.
- Incidence and Treatment of Rare Lesions of the Uterus and Vagina. ROBERT E. FRICKE, M.D., MARTIN VAN HERIK, M.D., AND E. H. SOULE, M.D.
- Surgery and Radiation of Cancer in the Female Breast. FREDERICK W. O'BRIEN, Sr., M.D., AND FREDERICK W. O'BRIEN, Jr., M.D.

Thursday, December 17**SECTION A: 10:30 A.M.-12:00 Noon**

- Symposium on Low Back Pain. EARL BARTH, M.D., Moderator. JOHN WINSTON, M.D., ROBERT MORETON, M.D., CHARLES L. EWING, Attorney, R. M. POTTER, M.D., AND J. R. NORCROSS, M.D.

SECTION B: 10:30 A.M.-12:30 P.M.

- Radiation Units and Radiation Instruments. HERBERT M. PARKER, M.S.C.

- Surface Dose. ELIZABETH FOCHT, B.A.
- Intensity versus Dose. JOHN LAUGHLIN, Ph.D.
- Internally Administered Radioisotopes. L. D. MARINELLI, M.A.
- Report of International Commission on Radiological Protection and International Commission on Radiological Units. L. S. TAYLOR, Ph.D.

AFTERNOON SESSION: 2:00 P.M.-4:00 P.M.

- Physical Aspects of Rotating Telecobalt Equipment. C. B. BRAESTRUP, B.S., AND R. MOONEY, M.A.
- Principles of Supervoltage Rotation Therapy. MILTON FRIEDMAN, M.D., GERALD J. HINE, Ph.D., AND JOSEPH DRESNER, M.S.C.
- Dosage Determinations for Horizontal Rotation Therapy. EDITH H. QUIMBY, Sc.D., CHARLES SOIFER, B.A., AND VICTORIA DE CASTRO, B.A.
- The Calculation of Rotation Therapy Tumor Doses at 250 kv. by Means of the Intensity of Transmitted Radiation. ROBERT ROBBINS, M.D., AND JEAN MESZAROS, M.S.

ANNUAL BANQUET: 7:00 P.M.**Friday, December 18****SECTION A: 10:00 A.M.-12:30 P.M.**

- Intramural Hematoma of the Duodenum: A Diagnostic Roentgen Sign. BENJAMIN FELSON, M.D., AND EMANUEL J. LEVIN, M.D.
- Volvulus of the Colon. LEO S. FIGIEL, M.D., AND STEVEN J. FIGIEL, M.D.
- Polypoid Diseases of the Stomach. RICHARD E. OTTMAN, M.D., AND JOHN H. WOODRUFF, JR., M.D.
- Factors Influencing the Roentgen Visualization of the Gastric Mucosa. EVERETT L. PIRKEV, M.D., PETER K. KNOEFEL, M.D., AND LAWRENCE A. DAVIS, M.D.
- Roentgen Manifestations of Relapsing Pancreatitis and Associated Conditions. MAXWELL H. POPPEL, M.D.
- The Potential Hazard of Enemas in Patients With Hirschsprung's Disease. HOWARD L. STEINBACH, M.D., ROBERT H. ROSENBERG, M.D., AND MOSES GROSSMAN, M.D.

SECTION B: 10:30 A.M.-12:30 P.M.

- Comparative Survival Times of X-ray Treated Versus P³² Treated Patients with Chronic Leukemias Under the Program of Titrated, Regularly Spaced Total-Body Irradiation. EDWIN E. OSGOOD, M.D., ARTHUR J. SEAMAN, M.D., AND HAROLD TIVEY, M.D.
- Spleen Protection Studies in Irradiated Animals. LEONARD J. COLE AND M. C. FISHLER.
- Dosimetry of Localized Beams. G. S. SHAPIRO, M.S., J. OVADIA, Ph.D., AND J. S. LAUGHLIN, Ph.D.
- A Large Ionization Chamber for Integral Dose Measurements in Betatron Radiation Therapy. JOHN W. BEATTIE, B.S., WALTER J. HENDERSON, B.S., WALTER S. MOOS, Ph.D., AND LEWIS L. HAAS, M.D.

ANNOUNCEMENTS AND BOOK REVIEWS

RADIOLOGY SECTION, CALIFORNIA MEDICAL ASSOCIATION

The newly elected officers of the Radiology Section of the California Medical Association are: Chairman, Calvin L. Stewart, M.D., of San Diego; Secretary, H. R. Morris, M.D., 1027 D St., San Bernardino; Assistant Secretary, M. A. Sisson, M.D., 450 Sutter St., San Francisco 8.

RADIOLOGICAL SOCIETY OF LOUISIANA

At the 1953 Annual Meeting of the Louisiana State Medical Society, the radiologists of the state met and reorganized their association, changing the name to Radiological Society of Louisiana. Officers are Henry M. Duhe, M.D., of New Orleans, President; G. M. Riley, M.D., of Shreveport, Vice-President; J. T. Brierre, M.D., 700 Audubon Bldg., New Orleans, Secretary-Treasurer.

OREGON RADIOLOGICAL SOCIETY

New officers of the Oregon Radiological Society, elected at their last Annual Meeting, are: President, J. Richard Raines, M.D., of Portland; Vice-President, Clay A. Racely, M.D., of Eugene; Secretary-Treasurer, John Wayne Loomis, M.D., 919 Taylor St. Bldg., Portland 5; Executive Committeeman, Wayne G. Ericksen, of Portland. Dr. Ivan Woolley was renominated as Councillor.

PENNSYLVANIA RADIOLOGICAL SOCIETY

At the Annual Meeting of the Radiological Society of Pennsylvania, Dr. Joseph T. Danzer of Oil City was elected President; Dr. George W. Chamberlin of Reading, President-Elect; Dr. Carl B. Lechner of Erie, Editor; Dr. James M. Converse, 416 Pine St., Williamsport 8, Secretary-Treasurer. The next Annual Meeting of the Society will be held at the Bedford Springs Hotel, Bedford, Penna., May 14 and 15, 1954.

A BERYLLIUM CASE REGISTRY

With funds supplied by the Atomic Energy Commission, it is planned to develop a beryllium case registry at the Massachusetts General Hospital. The purpose is to enable a study of the epidemiology of this disease, evaluation of the beryllium hazard of incriminated operations, and dissemination of knowledge of the clinical course of beryllium poisoning especially in relationship to its medical management. The material collected is to be available for study, and from time to time data will be sent to participating physicians, summarizing facts that have been established.

It is hoped that physicians, roentgenologists, and

pathologists, who have knowledge of cases of beryllium poisoning, will wish to participate in making this beryllium case registry complete. It is planned to keep cases entered in the registry anonymous.

Any correspondence will be welcomed. It should be addressed to Harriet L. Hardy, M.D., Occupational Medical Clinic, Massachusetts General Hospital, Boston 14, Mass.

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES

W. W. Grigorieff, Director of the Institute of Science and Technology of the University of Arkansas, has been named Chairman of the University Relations Division of the Oak Ridge Institute of Nuclear Studies, succeeding Russell S. Poor, who has left Oak Ridge to become Provost of the University of Florida Health Center. The University Relations Division administers a number of fellowship programs for the Atomic Energy Commission and with Oak Ridge National Laboratory carries out research participation, Oak Ridge graduate and other programs of interest to universities.

AMERICAN CANCER SOCIETY EDUCATION COLOR TELEVISION BROADCASTS

The American Cancer Society, in conjunction with the facilities of the Columbia Broadcasting System TV Network, will produce during 1953-54 a series of closed-circuit color television programs for doctors in general practice.

The long-range objective of this project is to enlarge the pattern of nation-wide postgraduate medical education by inaugurating a pilot project of color television clinical presentations oriented to county medical societies. The immediate objective is to improve cancer cure rates by making available to the general practitioner knowledge of the most effective technics in diagnosing and treating early cancer.

There will be a series of thirty, one-hour closed-circuit color television broadcasts which will be viewed by practitioners in six major cities in the northeast—Boston, Philadelphia, Pittsburgh, Detroit, Toledo, and New York—with the possibility that other cities will be added as the series progresses. All programs will originate in New York, from the Columbia-Presbyterian Medical Center and from the Memorial Center. The tentative starting date for the series is Wednesday, Oct. 21, 5:00 to 6:00 P.M., from Frances Delafield Hospital at Columbia University. Programs will be broadcast on alternate Wednesdays up to Dec. 2, after which they will be presented weekly.

Each program will be viewed at the receiving end on the new Giant Color Television Projection Screen

(4½' × 6') which was demonstrated publicly for the first time at the recent American Medical Association meeting in New York. In the New York area, the receiver will be located at The New York Academy of Medicine.

Approximately 3,000 physicians will view the programs as they are broadcast. This represents the total number which the receivers at the outlet cities can accommodate (500 per receiver). The programs will be Color Kinescoped and the Kinescopes will ultimately be made available to local medical societies through regional and state offices of the American Cancer Society.

Books Received

Books received are acknowledged under this heading and such notice may be regarded as recognition of the courtesy of the sender. Reviews will be published in the interest of our readers and as space permits.

ROENTGEN DIAGNOSIS OF THE HEART AND GREAT VESSELS. BY ERICH ZDANSKY, M.D., Professor of Roentgenology, University of Vienna, and Director of the Central Roentgen Institute of the Allgemeinen Krankenhaus. Translated by LINN J. BOYD, M.D., F.A.C.P., Professor and Director of Medicine, the New York Medical College, Flower and Fifth Avenue Hospitals. A volume of 500 pages, with 334 figures. Published by Grune & Stratton, New York, N. Y. First American Edition, 1953. Price \$15.50.

ATOMIC MEDICINE. Edited by CHARLES F. BEHRENS, M.D., Rear Admiral, MC, U. S. Navy, Staff Medical Officer, Eastern Sea Frontier; formerly Director, Atomic Defense Division, Bureau of Medicine and Surgery, Navy Department, and Commanding Officer, Naval Medical Research Institute, National Naval Medical Center, Bethesda, Md. A volume of 632 pages, with numerous illustrations. Published by the Williams & Wilkins Co., Baltimore, Md. Second edition, 1953. Price \$11.00.

SYMPOSIUM ON CHROMOSOME BREAKAGE (held at the John Innes Horticultural Institution, June 9-11, 1952). Supplement to *Heredity*, Volume 6. A volume of 315 pages, with numerous illustrations. Published by Charles C Thomas, Springfield, Ill., 1953. Price \$7.50.

FOURTEENTH SEMI-ANNUAL REPORT OF THE ATOMIC ENERGY COMMISSION. A booklet of 98 pages. Published by the United States Government Printing Office, Washington, D. C., July 1953.

ENCYCLOPÉDIE ÉLECTRO-RADIOLOGIQUE: RADIO-AGNOSTIC (Volume II). By various authors.

Published under the direction of Robert Coliez, Médecin Électro-radiologiste des Hôpitaux de Paris. A volume of 709 pages with numerous illustrations. *Encyclopédie Médico-Chirurgicale*, 18, rue Séguier, Paris, 1953.

Book Reviews

MAN'S BACK. BY THEODORE A. WILLIS, M.D., F.A.C.S., Formerly Head, Department of Orthopedic Surgery, St. Luke's Hospital, Consulting Orthopedic Surgeon, U. S. P. H. S. Hospital, Cleveland, Ohio; Member, The American Orthopedic Association, The American Academy of Orthopedic Surgeons, The Clinical Orthopedic Society, Société Internationale de Chirurgie Orthopédique et de Traumatologie. A volume of 162 pages with 210 illustrations. Published by Charles C Thomas, Springfield, Ill., 1953. Price \$9.50.

This monograph on "Man's Back" is an expression of the author's personal opinions, based upon his own experience and an accumulation, over the years, of facts and impressions acquired from innumerable sources. He admits at the outset that no effort has been made to trace the opinions thus derived back to their sources and, carrying this idea to its logical conclusion, he has omitted any references to the literature in the form of bibliographies or author indexes.

The first three chapters of the work are devoted, in turn, to the embryology of the back, its anatomy, and vertebral anomalies and developmental defects. In these will be found the fundamental knowledge upon which all other studies must be based. A fourth chapter takes up the mechanics of the back, and a fifth describes methods of examination and interpretation of symptoms. From this point, the author goes on to discuss back injuries, diseases and tumors of the back, and scoliosis. A short but valuable chapter is concerned with psychoneuroses and malingering. Chapters on physical therapy and treatment conclude the monograph. The operative descriptions are brief, and no attempt is made to go into the intricacies of technique.

This work is a valuable addition to the literature, particularly so because it makes available the lifetime accumulation of knowledge on an important subject by a man whose eminence in the field is universally recognized. The book is attractively printed and bound. The illustrations are well chosen and of good technical quality.

FUNDAMENTALS OF CLINICAL CANCER, WITH EMPHASIS ON EARLY DIAGNOSIS AND TREATMENT. BY LEONARD B. GOLDMAN, M.D., Clinical Professor of Radiotherapy, New York Medical College, Flower and Fifth Avenue Hospitals; Chairman, Tumor Conference, and Director, Radiation Therapy Department, Queens General Hospital; Consultant Radiation Therapist, Flushing, Rockaway Beach,

and Triboro Hospitals, New York City. A volume of 312 pages, with 221 illustrations. Published by Grune & Stratton, Inc., 381 Fourth Ave., New York, N. Y., 1953. Price \$8.75.

In a concise and simply written book, Dr. Goldman has summarized his conclusions from an experience in treating 10,000 cancer patients in the past twenty years. Indeed, its conciseness in places is carried to such an extent that it constitutes a fault. In other places there is a frank deviation from accepted ideas. For example, in Chapter 8, on "Tumors of the Gynecologic Tract," Stage II cancer of the cervix is defined as "invasion of the musculature of the cervix."

This book commits many grave errors of omission and fewer but not less important errors of commission. It is said to have been written "for all physicians who diagnose and treat cancer," with the basic intent of making "every reader early cancer-minded as well as cancer-minded early." This is a good thought, and the book, in spite of its shortcomings, might serve well as a quick reference for those who are not directly concerned in the definitive diagnosis and treatment of cancer.

THE BREAST IN ROENTGEN DIAGNOSIS. By RAUL A. LEBORGNE, M.D., Head of the Radiologic Department of Instituto de Radiología y Centra de Lucha contra el Cáncer, Hospital Pereira Rosell, Montevideo, Uruguay. English translation by LUCY CROCKER DE LEBORGNE. A volume of 194 pages, with 307 illustrations. Published by Impresora Uruguaya S.A., Juncal 1511 Montevideo, Uruguay, 1953.

This book is intended to show the value of roentgenographic examination in the diagnosis of breast lesions, especially cancer. A short explanation of the technic of plain and contrast mammography and intraductal biopsy is given, followed by a description of the radiographic appearance of the breast in different periods of life. The main part of the book, as might be expected, concerns carcinoma, though fibrocystic mastopathy, fibroadenoma, mastitis, and other less frequent conditions are also included. The text is concise and reduced to a minimum, the illustrations numerous and well reproduced, making this book a well documented roentgenographic atlas of diseases of the breast.

RADIOLOGIE DU REIN ET DE L'URETERE. By R. GOUVERNEUR, Chirurgien de l'Hôpital Necker, Chef du service d'Urologie, P. PORCHER, Radiologiste de l'Hôpital Saint-Antoine, and R. HICKEL, Radiologiste des Hôpitaux, Radiologiste du service d'Urologie de l'Hôpital Necker. A volume of 440 pages, with 412 figures. Published by Masson & Cie, Paris, 1953. Price 5,400 fr.

This monograph is intended as a complete treatise on radiologic study of the kidney and

ureter. The authors prepare their patients with castor oil for purgation the night before, followed by an enema with turpentine and cottonseed oil about four hours before examination. The various means of examination include simple films, intravenous or excretory urography, urographic nephrography, aortography, and pneumoretroperitoneum. Compression of the abdomen over the ureters is advocated during intravenous urography, but the compression is maintained only five to seven minutes. Special procedures under special conditions include retrograde pyelography with air, lumbar pyelography through a nephrostomy tube, and fistulography.

The radiologic anatomy of the kidney and ureter is described. This is followed by a discussion of the functional aspects of intravenous urography.

Renal anomalies are grouped according to the simple classification proposed by Papin. This includes three principal classes: anomalies of form and volume, anomalies of number, and anomalies of position with or without fusion. Anomalies of the ureter include duplications, bifurcations, and diverticula.

The ensuing chapters contain extensive discussion and illustrations of the urinary tract in pregnancy; dilatation of the calyces, renal pelvis and ureters; urinary calcification; tuberculous and non-tuberculous infections; cysts and tumors of the kidney, including hydatid cysts; renal and ureteral traumatic lesions and fistulas. Brief mention is made of less common conditions, as renal infarct, perirenal hematoma, and renal arterial aneurysm. A moderately extensive bibliography is appended for further reference.

Considered *in toto*, this book contains much valuable information for those interested in roentgenography of the kidneys and ureters. The discussion is pertinent and the illustrations are carefully selected.

DAS ULKUS DES MAGENS UND ZWÖLFFINGERDARMS, ALS PROBLEM EINES SCHUTZSTOFFMANGELS. By DR. H. RAMB, Chefarzt der Chirurg. Abteilung am Laurentius-Hospitale, Essen-Steele. A monograph of 68 pages, with 28 illustrations. Published by Georg Thieme, Stuttgart, 1953. Agents for U. S. A.: Grune & Stratton, Inc., New York, N. Y. Price DM 6.50.

In the western industrial section of Germany (Ruhr), gastric and duodenal ulcers comprise 2.5 to 3 per cent of disabling diseases of men and about 1 per cent of disabling diseases of women. Furthermore, while the average yearly disability for all diseases is twenty-eight days, the disability for peptic ulcer averages forty-six days. At the author's clinic, about 300 to 350 stomach resections are done every year. This disease, therefore, assumes great social and economic significance. In this monograph, some views as to the origin of these ulcers are set forth.

A peptic ulcer can develop only where there is active gastric secretion, that is, in the stomach or the first part of the duodenum, but it may arise in a Meckel's diverticulum if the latter contains ectopic gastric mucosa. In the duodenum a peptic ulcer will arise only in the proximal part, perhaps up to the papilla of Vater. In the distal half of the stomach, the ulcer is almost always on the lesser curvature. In the proximal half, it may be located along the anterior or, more often, along the posterior wall. The author believes that an ulcer almost always develops first on the lesser curvature. It may spread symmetrically in a band-like fashion over the anterior and posterior surface of the stomach. The mid-portion along the lesser curvature may then heal, leaving two ulcers, one on the anterior and one on the posterior wall ("kissing ulcers") which, if the stomach is cut open along the greater curvature and spread out, appear to be quite symmetrical. The one on the anterior surface shows a greater tendency to healing, often leaving only the one along the posterior surface. A symmetrical distribution is also often found in the duodenum, but duodenal "kissing ulcers" are held to be due, for the most part, to direct contact. Probably certain osmotic alterations and disturbances in the ion concentration of the ulcer cause similar changes in the mucous membrane lying in contact with it and render it less resistant to the digestive action of the gastric secretion. While in a normal stomach or duodenum a mechanical or chemical erosion of the mucous membrane heals very rapidly, in the ulcer patient, the author believes, some protective substance is missing. Thus, the digestive action of the gastric secretion upon the mucous membrane is not sufficiently impeded and an ulcer develops.

Many etiologic factors that have been mentioned as possible causes of a peptic ulcer are still debatable, such as diet, smoking, seasonal influences, focal infection (particularly in the oral cavity), psychic factors, and neurogenic and vascular influences. The author has been especially interested in the last two, and has in a number of cases severed the nerves and some of the vessels which locally supply the lesser curvature of the stomach and the duodenum. The operation was a failure, however, and subsequent resection was required.

Hyperacidity of the gastric secretion is usually present, particularly in the acute, active cases, but it cannot be regarded as a cause of the ulcer, since some active cases show anacidity. Furthermore, the digestive action of pepsin reaches its optimum at normal acidity and diminishes as the acidity increases.

An analysis of the various factors leads to the conclusion, as stated above, that in the ulcer patient some protective substance, which normally prevents the auto-digestion of the mucous membrane, must be missing. A causative treatment will not be possible until this substance is discovered. Careful examination and analysis of the blood serum

of ulcer patients and comparison with the serum of normal persons are suggested as a possible means of discovering the missing protective factor. In the meantime, the author believes that of all the treatments advocated, the resection of slightly more than 50 per cent of the stomach gives the best chances of a permanent cure.

RÖNTGENUROSKOPIE. NIERENBECKEN UND -KELCHE. HARNLEITER, BLASE, HARNRÖHRE. By Dr. MED. HABIL. G. W. GÜNTHER, Mannheim. A monograph of 45 pages, with 86 illustrations. Published by Georg Thieme, Stuttgart, 1952. Distributor for U. S. A.: Grune & Stratton, Inc., New York, N. Y. Price DM 13.50.

The term roentgenuroscopy signifies the fluoroscopic examination of the urinary tract during both excretory and retrograde pyelography. Günther claims that, by combining this procedure with deliberately aimed and timed roentgenograms, one obtains refinement in diagnosis not possible with the routine, essentially blind, radiographic methods. A fibrous band, for example, may be apparent only fluoroscopically, because the urinary retention is fleeting and the impression on the ureter or pelvis transient. Nevertheless, the band—or its counterpart, the aberrant vessel—may be the obscure provocative factor in renal colic, hematuria, infection, and stone formation. A fibrous band is fixed in position, may be single or double, and is best demonstrated with the renal pelvis distended with the contrast medium.

Fluoroscopy reveals the renal calyces and pelvis to be contractile and a functional unit with the ureter. The peristaltic spindle starts in the pelvis, which may contract physiologically to the size of the ureter, and then progresses down the latter. Pathologic contraction bands also occur on either a reflex or a neurogenic basis. Purely spastic constrictions are considered to be just as much a pathologic finding as the fibrous bands which they mimic.

Transient ureteral kinks and spasms are in the realm of functional pathology, since there is correlation with pain and hematuria. The spasmophilia, perhaps associated with ureteral dyskinesia, can be the result of too rapid injection of the medium in a retrograde study, of pregnancy, of Basedow's disease, of a regional vascular crossing, of a reflex due to infection elsewhere, or of pyelitis.

Bogard once claimed that all ureteral kinks are due to aberrant vessels. According to Günther, they rarely are. He regards kinking as a problem of tonus associated with either peristalsis, position, or remote disease. Inadequate contraction of the longitudinal muscle of the ureter is the presumed mechanism.

Günther considers roentgenuroscopy the cheapest, surest, and most convenient way to find obscure and radiolucent calculi. Should one be hypothesizing renal colic on a reflex spastic basis, it is of course

important to rule out all other disease. The case for fluoroscopy in the finding of calculi is not strong; the stones illustrated should have been easily recognized by ordinary methods.

GRUNDRISSE DER ELECKROKYMOGRAPHIE: PHASEN-ANALYSE UND RAUMKYMOGRAPHIE DES HERZENS. By PRIV.-DOZ. DR. K. HECKMANN, München. A monograph of 36 pages, with 54 illustrations. Published by Georg Thieme, Stuttgart, 1952. Distributors for U. S. A.: Grune & Stratton Inc., New York, N. Y. Price DM 6.60.

With electrokymography now becoming widely used by cardiologists, a brief atlas to aid in the interpretation of the waves is offered by Doctor Heckmann. The illustrations are idealized line drawings and not actual recordings. For the latter, the author uses a unit commercially available in Munich, which simultaneously records the heart sounds.

Part I consists of illustrations of normal ventricular waves, normal atrial waves, and normal arterial waves with their variations. These are, of course, identical with the corresponding waves in a roentgenkymogram. Pathologic ventricular waves are then shown for such conditions as ventricular dilatation, cardiac hyperactivity, obliterative pericarditis, mitral stenosis, heart block, and aortic sclerosis. The curves are named descriptively as plateau-like, sinusoidal, flame-like, double-peaked. Only two abnormal atrial waves are reproduced, one for mitral insufficiency and the other for absolute arrhythmia. Among the arterial curves are those for pendulum motion, heart failure, and aortic sclerosis.

Phase analysis concerns itself with correlation of the curves with the sequence of events in the cardiac cycle in terms of time. An additional study in this analysis is the effect of shift in position of the heart during systole and diastole. The influence of positional change, both in health and in several diseases, is demonstrated.

In Memoriam

MARGARET CHRISTINE TOD, F.R.C.S.E.,
F.F.R.

Dr. Margaret Christine Tod, widely known for her work in the field of radiotherapy, died on July 26, 1953, at the home of her sister in Edinburgh, Scotland. She was sixty years of age, and throughout a

long illness she faced the knowledge of the inevitable outcome with quiet courage.

Miss Tod took up nursing during the First World War, having converted her home into a convalescent hospital for Naval casualties. In 1919 she began her medical studies at the University of Edinburgh and graduated M.B., Ch.B. in 1924 with First Class Honours. Her many prizes included the Ettles Scholarship and Leslie Gold Metal for the most distinguished student of the year, an honor never previously awarded to a woman student. After postgraduate resident posts and a visit to clinics in America, she was elected a Fellow of the Royal College of Surgeons of Edinburgh and appointed honorary assistant surgeon to the Bruntfield Hospital for Women and the Edinburgh Royal Sick Childrens' Hospital.

While practising surgery she became increasingly interested in radiation therapy and the problems of malignant disease, and in 1937, after working in the Radiotherapy Department at Edinburgh Royal Infirmary, she joined the staff of the Holt Radium Institute, Manchester, as Deputy Director under Ralston Paterson. She rapidly acquired an international reputation, and though she was perhaps best known for her work on cancer of the uterine cervix, her many published papers covered the entire field of radiation therapy. When the National Radium Commission was dissolved in 1948, Miss Tod had been its secretary for eighteen months and from the Commission's records she published a most valuable analysis on "The Extent to which Cancer Patients in Great Britain Receive Radiotherapy." She was also the Secretary of the Royal Society of Medicine's Section of Radiology, a Fellow of the Faculty of Radiologists, and editor of the Faculty's Journal. In 1951 she was awarded the Röntgen Medal of the British Institute of Radiology as a tribute to her many contributions to radiotherapy.

Though she visited the major European centers with some regularity, she also made many close friends during her lecture tours, sponsored by the British Council, in Italy, Austria, and South America. Hers was a truly international circle of friends, who will all share the loss to her British colleagues.

Those who were privileged to work with her will remember M.C.T. most for her tireless energy, her quiet wisdom based on a wide and reliable experience, her kindly concern for her younger colleagues, and her ever-ready willingness to discuss their personal problems.

RADIOLOGICAL SOCIETIES: SECRETARIES AND MEETING DATES

Editor's Note: Secretaries of state and local radiological societies are requested to co-operate in keeping this section up-to-date by notifying the editor promptly of changes in officers and meeting dates.

RADIOLOGICAL SOCIETY OF NORTH AMERICA. *Secretary-Treasurer*, Donald S. Childs, M.D., 713 E. Genesee St., Syracuse 2, N. Y.

AMERICAN RADIUM SOCIETY. *Secretary*, Robert E. Fricke, M.D., Mayo Clinic, Rochester, Minn.

AMERICAN ROENTGEN RAY SOCIETY. *Secretary*, Barton R. Young, M.D., Germantown Hospital, Philadelphia 44, Penna.

AMERICAN COLLEGE OF RADIOLOGY. *Exec. Secretary*, William C. Stronach, 20 N. Wacker Dr., Chicago 6.

SECTION ON RADIOLOGY, A. M. A. *Secretary*, Paul C. Hodges, M.D., 950 East 59th St., Chicago 37.

Alabama

ALABAMA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, J. A. Meadows, Jr., M.D., Medical Arts Bldg., Birmingham 5.

Arizona

ARIZONA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, R. Lee Foster, M.D., 507 Professional Bldg., Phoenix. Annual meeting with State Medical Association; interim meeting in December.

Arkansas

ARKANSAS RADIOLOGICAL SOCIETY. *Secretary*, Fred Hames, M.D., Pine Bluff. Meets every three months and at meeting of State Medical Society.

California

CALIFORNIA MEDICAL ASSOCIATION, SECTION ON RADIOLOGY. *Secretary*, H. R. Morris, M.D., 1027 D St., San Bernardino.

EAST BAY ROENTGEN SOCIETY. *Secretary*, Dan Tucker, M.D., 434 30th St., Oakland 9. Meets monthly, first Thursday, at Peralta Hospital.

LOS ANGELES RADIOLOGICAL SOCIETY. *Secretary*, George Jacobson, M.D., 1200 North State St., Los Angeles 33. Meets monthly, second Wednesday, Los Angeles County Medical Association Bldg.

NORTHERN CALIFORNIA RADIOLOGICAL SOCIETY. *Secretary*, Richard C. Ripple, M.D., 1215 28th St., Sacramento. Meets at dinner last Monday of September, November, January, March, and May.

PACIFIC ROENTGEN SOCIETY. *Secretary*, L. Henry Garland, M.D., 450 Sutter St., San Francisco 8. Meets annually at time of California State Medical Association convention.

SAN DIEGO RADIOLOGICAL SOCIETY. *Secretary*, C. W. Bruner, M.D., 2456 Fourth Ave., San Diego 1. Meets first Wednesday of each month.

SAN FRANCISCO RADIOLOGICAL SOCIETY. *Secretary*, I. J. Miller, M.D., 2680 Ocean Ave., San Francisco 27. Meets quarterly, at the University Club.

SOUTH BAY RADIOLOGICAL SOCIETY. *Secretary*, William H. Graham, M.D., 634 E. Santa Clara St., San Jose 12. Meets monthly, second Wednesday.

X-RAY STUDY CLUB OF SAN FRANCISCO. *Secretary*, Wm. W. Saunders, M.D., VA Hospital, San Francisco 21. Meets third Thursday at 7:45, Lane Hall, Stanford University Hospital.

Colorado

COLORADO RADIOLOGICAL SOCIETY. *Secretary*, Wm. S. Curtis, M.D., Boulder Medical Center, Boulder. Meets monthly, third Friday, at University of Colorado Medical Center or Denver Athletic Club.

Connecticut

CONNECTICUT STATE MEDICAL SOCIETY, SECTION ON RADIOLOGY. *Secretary-Treasurer*, William A. Goodrich, M.D., 85 Jefferson St., Hartford 14. Meets bimonthly, second Wednesday.

CONNECTICUT VALLEY RADIOLOGICAL SOCIETY. *Secretary*, B. Bruce Alicandri, M.D., 20 Maple St., Springfield, Mass. Meets second Friday of October and April.

District of Columbia

RADIOLOGICAL SECTION, DISTRICT OF COLUMBIA MEDICAL SOCIETY. *Secretary*, Alvin C. Wyman, M.D., 5445 28th St., N.W., Washington. Meets third Wednesday, January, March, May, and October, at 8:00 P.M., in Medical Society Library.

Florida

FLORIDA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, A. Judson Graves, M.D., 2002 Park St., Jacksonville. Meets in April and in November.

GREATER MIAMI RADIOLOGICAL SOCIETY. *Secretary*, E. Hampton Bryson, M.D., 273 Alhambra Circle, Coral Gables. Meets monthly, third Wednesday, 8:00 P.M., Veterans Administration Bldg., Miami.

Georgia

ATLANTA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Albert A. Rayle, Jr., M.D., 490 Peachtree St. Meets second Friday, September to May.

GEORGIA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Robert M. Tankesley, M.D., 218 Doctors Bldg., Atlanta. Meets in November and at the annual meeting of the State Medical Association.

RICHMOND COUNTY RADIOLOGICAL SOCIETY. *Secretary*, Wm. F. Hamilton Jr., M.D., University Hospital, Augusta.

Hawaii

RADIOLOGICAL SOCIETY OF HAWAII. *Secretary*, Philip S. Arthur, M.D., Suite 42, Young Hotel Bldg., Honolulu. Meets third Friday of each month.

Illinois

CHICAGO ROENTGEN SOCIETY. *Secretary*, Elbert K. Lewis, M.D., 6337 S. Harvard Ave., Chicago 21. Meets at the University Club, second Thursday of October, November, January, February, March, and April at 8:00 P.M.

ILLINOIS RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Stephen L. Casper, M.D., Physicians and Surgeons Clinic, Quincy.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON RADIOLOGY. *Secretary*, George E. Irwin, Jr., M.D., 427 N. Main St., Bloomington.

Indiana

INDIANA ROENTGEN SOCIETY. *Secretary-Treasurer*, John A. Robb, M.D., 23 East Ohio St., Indianapolis. Annual meeting in May.

Iowa

IOWA RADIOLOGICAL SOCIETY. *Secretary*, James T. McMillan, M.D., 1104 Bankers Trust Bldg., Des Moines. Meets during annual session of State Medical Society, and holds a scientific session in the Fall.

Kansas

KANSAS RADIOLOGICAL SOCIETY. *Secretary*, Willis L. Beller, M.D., 700 Kansas Ave., Topeka. Meets in the Spring with the State Medical Society and in the Winter on call.

Kentucky

KENTUCKY RADIOLOGICAL SOCIETY. *Secretary*, Everett L. Pirkey, M.D., Louisville General Hospital. Meets monthly, second Friday, at Seelbach Hotel, Louisville.

Louisiana

ORLEANS PARISH RADIOLOGICAL SOCIETY. *Secretary*, Joseph V. Schlosser, M.D., Charity Hospital of Louisiana, New Orleans 13. Meets second Tuesday of each month.

RADIOLOGICAL SOCIETY OF LOUISIANA. *Secretary-Treasurer*, J. T. Brierre, M.D., 700 Audubon Bldg., New Orleans.

SHREVEPORT RADIOLOGICAL CLUB. *Secretary*, W. R. Harwell, M.D., 608 Travis St. Meets monthly September to May, third Wednesday.

Maine

MAINE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Hugh Allan Smith, M.D., Eastern Maine General Hospital, Bangor. Meets three times a year—Spring, Summer, and Fall.

Maryland

BALTIMORE CITY MEDICAL SOCIETY, RADIOLOGICAL SECTION. *Secretary-Treasurer*, H. Leonard Warres, M.D., 2337 Eutaw Place, Baltimore 17. Meets third Tuesday, September to May.

MARYLAND RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, H. Leonard Warres, M.D., 2337 Eutaw Place, Baltimore 17.

Michigan

DETROIT X-RAY AND RADIUM SOCIETY. *Secretary*,

E. F. Lang, M.D., Harper Hospital, Detroit 1. Meets first Thursday, October to May, at Wayne County Medical Society club rooms.

Minnesota

MINNESOTA RADIOLOGICAL SOCIETY. *Secretary*, John R. Hodgson, M.D., The Mayo Clinic, Rochester. Meets in Spring and Fall.

Mississippi

MISSISSIPPI RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, John W. Evans, M.D., 117 N. President St., Jackson, Miss. Meets monthly, third Tuesday, at 6:30 P.M., at the Rotisserie Restaurant, Jackson.

Missouri

RADIOLOGICAL SOCIETY OF GREATER KANSAS CITY. *Secretary*, James E. McConchie, M.D., First National Bank Bldg., Independence, Mo. Meets last Friday of each month.

ST. LOUIS SOCIETY OF RADIOLOGISTS. *Secretary*, Francis O. Trotter, Jr., M.D., 634 North Grand Blvd., Meets on fourth Wednesday, October to May.

Montana

MONTANA RADIOLOGICAL SOCIETY. *Secretary*, Grant P. Raitt, M.D., 413 Medical Arts Bldg., Billings. Meets annually.

Nebraska

NEBRASKA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, James F. Kelly, Jr., M.D., 816 Medical Arts Bldg., Omaha. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

New England

NEW ENGLAND ROENTGEN RAY SOCIETY. *Secretary*, Stanley M. Wyman, M.D., Massachusetts General Hospital, Boston 14. Meets monthly on third Friday, at the Harvard Club, Boston.

New Hampshire

NEW HAMPSHIRE ROENTGEN SOCIETY. *Secretary*, Albert C. Johnston, M.D., 127 Washington St., Keene.

New Jersey

RADIOLOGICAL SOCIETY OF NEW JERSEY. *Secretary*, Salomon Silvera, M.D., 921 Bergen Ave., Jersey City. Meets at Atlantic City at time of State Medical Society and midwinter in Elizabeth.

New York

BUFFALO RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Mario C. Gian, M.D., 610 Niagara St., Buffalo 1. Meets second Monday, October to May.

CENTRAL NEW YORK ROENTGEN SOCIETY. *Secretary*, Dwight V. Needham, M.D., 608 E. Genesee St., Syracuse 2. Meets in January, May, and October.

KINGS COUNTY RADIOLOGICAL SOCIETY. *Secretary*, Solomon Maranov, M.D., 1450 51st St., Brooklyn 19. Meets fourth Thursday, October to April (except December), at 9:00 P.M., Kings County Medical Bldg.

NASSAU RADIOLOGICAL SOCIETY. *Secretary*, Frank Huber, M.D., 131 Fulton Ave., Hempstead, N. Y. Meets second Tuesday, February, April, June, October, and December.

NEW YORK ROENTGEN SOCIETY. *Secretary*, Jacob R. Freid, M.D., 1049 Park Ave., New York.

NORTHEASTERN NEW YORK RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Donald H. Baxter, M.D., Albany Hospital, Albany. Meets in the capital area second Wednesday, October, November, March, and April. Annual meeting in May or June.

ROCHESTER ROENTGEN-RAY SOCIETY. *Secretary-Treasurer*, A. Gordon Ide, M.D., 277 Alexander St. Meets at Strong Memorial Hospital, 8:15 P.M., last Monday of each month, September through May.

WESTCHESTER RADIOLOGICAL SOCIETY. *Secretary*, Clifford C. Baker, M.D., Harwood Bldg., Scarsdale. Meets third Tuesday of January and October and at other times as announced.

North Carolina

RADIOLOGICAL SOCIETY OF NORTH CAROLINA. *Secretary*, Waldemar C. A. Sternbergh, M.D., 1400 Scott Ave., Charlotte 2. Meets in April and October.

North Dakota

NORTH DAKOTA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, H. Milton Berg, M.D., Quain & Ramstad Clinic, Bismarck. Meets in the Spring with State Medical Association; in Fall or Winter on call.

Ohio

OHIO STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, M. M. Thompson, Jr., M.D., 316 Michigan St., Toledo. Meets with State Medical Association.

CENTRAL OHIO RADIOLOGICAL SOCIETY. *Secretary*, Frank A. Riebel, M.D., 15 W. Goodale St., Columbus. Meets second Thursday, October, December, February, April, and June, 6:30 P.M., Columbus Athletic Club, Columbus.

CLEVELAND RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Mortimer Lubert, M.D., Heights Medical Center Bldg., Cleveland Heights 6. Meets at 6:45 P.M. on fourth Monday, October to April, inclusive.

GREATER CINCINNATI RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Chapin Hawley, M.D., 927 Carew Tower, Cincinnati 2. Meets first Monday of each month, September to June, at Cincinnati General Hospital.

MIAMI VALLEY RADIOLOGICAL SOCIETY. *Secretary*, W. S. Koller, M.D., 60 Wyoming St., Dayton. Meets monthly, second Friday.

Oklahoma

OKLAHOMA STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, John R. Danstrom, M.D., Medical Arts Bldg., Oklahoma City.

Oregon

OREGON RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, John Wayne Loomis, M.D., 919 Taylor Street Bldg., Portland 5. Meets monthly, second Wednesday, October to June, at 8:00 P.M., University Club, Portland.

Pacific Northwest

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Sydney J. Hawley, M.D., 1320 Madison St., Seattle 4. Meets annually in May.

Pennsylvania

PENNSYLVANIA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, James M. Converse, M.D., 416 Pine St., Williamsport 8. Meets annually.

PHILADELPHIA ROENTGEN RAY SOCIETY. *Secretary*, Herbert M. Stauffer, M.D., Temple University Hospital, Philadelphia 40. Meets first Thursday of each month at 5:00 P.M., from October to May, in Thompson Hall, College of Physicians.

PITTSBURGH ROENTGEN SOCIETY. *Secretary-Treasurer*, Donald H. Rice, M.D., 4800 Friendship Ave., Pittsburgh 24. Meets monthly, second Wednesday, at 6:30 P.M., October to May, at Webster Hall.

Rocky Mountain States

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Maurice D. Frazer, M.D., 1037 Stuart Bldg., Lincoln, Nebr.

South Carolina

SOUTH CAROLINA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, William A. Klauber, M.D., Self Memorial Hospital, Greenwood. Meets with State Medical Association in May.

South Dakota

RADIOLOGICAL SOCIETY OF SOUTH DAKOTA. *Secretary-Treasurer*, Donald J. Peik, M.D., 303 S. Minnesota Ave., Sioux Falls. Meets during annual meeting of State Medical Society.

Tennessee

MEMPHIS ROENTGEN CLUB. *Secretary*, Harvey Thompson, M.D., 899 Madison Ave. Meets first Monday of each month at John Gaston Hospital.

TENNESSEE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, J. Marsh Frère, M.D., Newell Hospital, Chattanooga 2. Meets annually with State Medical Society in April.

Texas

DALLAS-FORT WORTH ROENTGEN STUDY CLUB. *Secretary*, Claude Williams, M.D., Fort Worth. Meets monthly, third Monday, in Dallas odd months, Fort Worth even months.

HOUSTON RADIOLOGICAL SOCIETY. *Secretary*, Harry Fishbein, M.D., 324 Medical Arts Bldg., Houston 2.

SAN ANTONIO-MILITARY RADIOLOGICAL SOCIETY. *Secretary*, Hugo F. Elmendorf, Jr., M.D., 730 Medical Arts Building, San Antonio 5, Texas. Meets at Brook Army Medical Center, the first Monday of each month.

TEXAS RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, R. P. O'Bannon, M.D., 650 Fifth Ave., Fort Worth. Next meeting Jan. 29-30, 1954, Dallas.

Utah

UTAH STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Angus K. Wilson, M.D., 343 S. Main St., Salt Lake City 1. Meets third Wednesday, January, March, May, September, November.

Virginia

VIRGINIA RADIOLOGICAL SOCIETY. *Secretary*, P. B. Parsons, M.D., 1308 Manteo St., Norfolk 7.

Washington

WASHINGTON STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, John N. Burkey, M.D., 555 Medical-Dental Bldg., Seattle. Meets fourth Monday, September through May, at College Club, Seattle.

West Virginia

WEST VIRGINIA RADIOLOGICAL SOCIETY. *Secretary*, W. Paul Elkin, 515-519, Medical Arts Bldg., Charleston. Meets concurrently with annual meeting of State Medical Society, and at other times as arranged by Program Committee.

Wisconsin

MILWAUKEE ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, Jerome L. Marks, M.D., 161 W. Wisconsin Ave., Milwaukee 1. Meets monthly on fourth Monday at the University Club.

SECTION ON RADIOLOGY, STATE MEDICAL SOCIETY OF WISCONSIN. *Secretary*, Abraham Melamed, M.D., 425 E. Wisconsin Ave., Milwaukee 2. Meets in October with State Medical Society.

UNIVERSITY OF WISCONSIN RADIOLOGICAL CONFERENCE. Meets first and third Thursday at 4 P.M., September to May, Service Memorial Institute.

WISCONSIN RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, W. W. Moir, M.D., Sheboygan Memorial Hospital, Sheboygan.

Puerto Rico

ASOCIACIÓN PUERTORRIQUEÑA DE RADIOLOGÍA. *Secretary*, Rafael A. Blanes, M.D., Box 9724 Santurce, Puerto Rico.

CANADA

CANADIAN ASSOCIATION OF RADIOLOGISTS. *Honorary Secretary-Treasurer*, D. L. McRae, M.D. *Asso-Hon. Secretary-Treasurer*, Guillaume Gill, M.D. *Central Office*, 1555 Summerhill Ave., Montreal 25. Quebec. Meets in January and June.

LA SOCIÉTÉ CANADIENNE-FRANÇAISE D'ELECTROLOGIE ET DE RADIOLOGIE MÉDICALES. *General Secretary*, Origène Dufresne, M.D., Institut du Radium, Montreal. Meets third Saturday of each month.

CUBA

SOCIEDAD DE RADIOLOGÍA Y FISIOTERAPIA DE CUBA. *Secretary*, Dr. Rafael Gómez Zaldivar. Offices in Hospital Mercedes, Havana. Meets monthly.

MEXICO

SOCIEDAD MEXICANA DE RADIOLOGÍA Y FISIOTERAPIA. *General Secretary*, Dr. Dionisio Pérez Cosío, Marsella 11. Mexico, D.F. Meets first Monday of each month.

PANAMA

SOCIEDAD RADIOLÓGICA PANAMEÑA. *Secretary-Editor*, Luis Arrieta Sánchez, M.D., Apartado No. 86, Panama, R. de P.



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ROENTGEN DIAGNOSIS

THE HEAD AND NECK

Introduction to Encephalography (Pneumoencephalography). Otto Schiersmann. Fortschr. a. d. Geb. d. Röntgenstrahlen, Ergänzungsband 64, pp. 1-136, 1952. (In German)

Encephalography, based on the replacement of the cerebrospinal fluid with gas, is firmly entrenched as an examination which directly visualizes the subarachnoid spaces and ventricular systems, thus allowing the diagnosis of lesions within the cranial cavity. Arteriography supplements but does not replace air studies.

The cerebrospinal fluid is produced by the choroid plexus and is resorbed in the subarachnoid spaces overlying the cerebral hemispheres. Within the brain the flow is from each lateral ventricle through the foramina of Monro, through the third ventricle, through the aqueduct into the fourth ventricle, thence into the cisterna magna via the foramen of Magendie and into the cisterna pontis via the foramina of Luschka. In a reverse direction, utilizing gravitational displacement, air introduced either by suboccipital or by lumbar tap replaces the fluid.

Available routes for the introduction of air are the ventricular, cisternal, and lumbar. While the last is the most uncomfortable to the patient, it is the easiest and most commonly used route. Side effects are troublesome but may be minimized. The more slowly the air is exchanged for the fluid, the less will be the discomfort. It is also to be noted that severe localized headache may occur at the site of disease, that patients with multiple sclerosis are apt to suffer greatly, and that the route is dangerous in the presence of increased intracranial pressure.

The six routine roentgen projections used by the author, and described in detail, are as follows:

1. *Anteroposterior Anterior Horn View:* The patient is supine, the brow is up, and the central ray is directed through the forehead.
2. *Horizontal Anterior Horn View:* A lateral decubitus projection to supplement the first view.
3. *Postero-anterior Posterior Horn View:* The patient is prone, the brow is down, and the central ray is directed through the occiput.
4. *Horizontal Posterior Horn View:* A lateral decubitus projection to supplement the third view.
5. *Right Lateral:* This shows the left ventricle.
6. *Left Lateral:* This shows the right ventricle.

Since the method of choice is lumbar encephalography and the air exchange is carried out under fluoroscopic control, one knows in advance whether or not replacement has been obtained. Obstructive hydrocephalus, for example, cannot be proved by lumbar encephalography, because one has simply non-filling of the ventricles, which may be incidental. External hydrocephalus usually allows ready ventricular filling. Childhood hydrocephalus is best studied *via* ventricular puncture.

Important in interpretation is the size of the ventricles. Of use here is the ventricular index, which is obtained by dividing the overall ventricular width into the overall skull width as seen in the anteroposterior view. An index of 1.8 to 3.0 signifies enlarged ventricles;

3.0 to 3.5 borderline; 3.5 to 4.0 normal; 4.0 to 7.0 small. Strikingly small lateral ventricles of normal form, in the absence of signs of cerebral edema, may be a feature of Kehr's syndrome. Enlarged ventricles signify disease in most instances, yet one must remember that a high normal ventricle may be larger than a small hydrocephalic one. Senility leads to shrinkage of the entire brain, with enlargement both of the sulci and of the ventricular system. One has an internal and an external hydrocephalus *ex vacuo*.

Encephalography has its greatest value when alterations in form, localized or generalized displacements, and unusual collections of air are demonstrated. Approximation of the anterior horns with an unduly high third ventricle is seen in agenesis of the corpus callosum. Arhinencephaly presents a peculiar fusion of the anterior horns. Spastic paraplegics, including those with normal intelligence, those with mental deficiency, and those with seizures, should all be checked encephalographically if only for prognosis and classification. One may find evidence of bilateral brain damage, unilateral damage, porencephaly hemiatrophy, and basal ganglia atrophy.

Although a normal encephalogram does not rule out a traumatic brain lesion, this type of study is still the best. Tentorial retraction of a ventricle may signify a glial scar. With post-traumatic atrophy, a ventricle tends to be displaced toward the diseased side, while in generalized atrophy both enlarge *ex vacuo*. Decreased ventricular size disappears with subsidence of acute edema. Shift of a ventricle also occurs in subdural hematoma, though this lesion is better shown arteriographically.

Brain tumor is the major indication for an air study. With this as a working diagnosis, ventriculography is essential. In general, supratentorial tumors displace one or more of the ventricles and infratentorial tumors yield hydrocephalus. Because the degree of distortion depends largely on edema, the roentgenogram does not reveal the size of the tumor. Localization of the mass involves only direct interpretation if simple statements are used in the report to the neurosurgeon. On the axial views a tumor may be central, lateral, parasagittal, or mid-line. In the lateral projection the tumor may be suprasellar, infrasellar, anterior temporal, subfrontal, anterior frontal, posterior frontal, frontoparietal, parietal, occipital, or posterior temporal. Many localizations, such as pineal, quadrigeminal, cerebellopontine, are characteristic radiographically and should be reported as such when recognized.

One hundred and eighty-six illustrations, including 152 roentgenograms.

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Vertebral Angiography and Its Diagnostic Significance. Th. Tiwisina. Fortschr. a. d. Geb. d. Röntgenstrahlen 77: 662-671, December 1952. (In German)

Vertebral angiography is especially valuable in demonstrating many of the lesions about the tentorium. In only about 10 to 20 per cent of cases is the posterior cerebral artery filled by injection of the internal carotid. Introducing the medium into the vertebral arteries has produced no ill effects in cases of increased intracranial pressure or edema of the brain. Limiting the injection

to 10 c.c. of Perabrodil M (45 per cent) minimizes the danger of rupture of the vessels, with extravasation due to increased pressure during the procedure, and resulting cerebellar apoplexy. There is a possible potential danger to the brain stem by hypoxemia in damaged areas, and it is also conceivable that the injection could contribute to thrombosis, but this has never been observed by the author.

The anatomical relationships of the injected vessels are discussed at length. The method is recommended for diseases of the arterial walls, including endarteritis and arteriosclerosis; for congenital and traumatic aneurysms; for hemangiomas and hemangioblastomas; for functional circulatory disturbances and vascular anomalies; for mass lesions of the cerebellum, basal ganglia, and third ventricle and cerebellopontine angle, and for supratentorial and subtentorial masses and aqueduct stenosis.

Views are made in three planes, fronto-occipital, basilar, and lateral. Case summaries and illustrations are given to clarify the details of diagnosis.

Twelve roentgenograms; 3 drawings.

E. W. SPACKMAN, M.D.
Fort Worth, Texas

The Radiological Diagnosis of Cerebro-Vascular Anomalies. Jean-Louis Léger. J. Canad. Assoc. Radiologists 3: 61-66, December 1952.

The presence of cerebral vascular anomalies may be confirmed by angiography. Except in cerebral arteriosclerosis, there are no specific contraindications to the procedure other than those for intravenous urography. Only one severe reaction occurred in over 440 cases seen in the Notre Dame Hospital, Montreal. In this instance, there was a recurrence of hemiplegia in a patient in whom the same accident had occurred twice before. The vascular anomalies most commonly demonstrated are aneurysms and angiomatous malformations (arteriovenous aneurysms).

Vascular malformations may be suspected when the plain skull roentgenogram shows the presence of bony erosion, calcium deposits, or enlargement of foramina or of blood vessel groups. Of aneurysms, only those in contact with the sella turcica produce bony erosion. Therefore, only aneurysms of the internal carotid proximal to the clinoid canal are likely to be detected on the plain film unless there is calcium in the wall. Judging from the author's series, the likelihood of finding calcium in an aneurysm is small. Of 23 aneurysms diagnosed, none showed calcium. On the contrary, calcified plaques are often detected in the carotid siphon of old patients without aneurysm.

Aneurysms are diagnosed by angiography without difficulty, but the neurosurgeon must know also: (1) the exact location of the aneurysm; (2) whether it has a well defined neck; (3) its direction in relation to the vessel from which it emerges. Angiograms are made in the following projections: lateral, anteroposterior, oblique through the orbit to elongate the siphon and its terminal branches. Both carotids are injected separately and, if nothing is found, the vertebral artery may be injected. If, however, the aneurysm is situated on the basilar artery or its branches, nothing is to be done, so the investigation need not be carried too far. The use of stereoscopic films doubles the dose of contrast substance and the author therefore does not think they are worthwhile. They do not replace films taken in different projections.

If the aneurysm is to be treated by ligation of the internal carotid, an injection of the opposite side should be done, with compression of the carotid on the side of the lesion, to anticipate the post-ligation result. Multiple aneurysms may be detected by injection of the whole vascular system. The author has not encountered at autopsy any aneurysms which were not found during angiography. It is believed, however, that a small percentage of non-filling aneurysms may exist.

Angiomatous malformations may give rise to the following roentgen signs: (1) calcium deposits, said to be visible in at least 50 per cent of the cases; (2) enlargement of their foramina by greatly dilated vessels; (3) prominence of the vascular grooves on the inner table of the skull. If the lesion is cortical and close to the bones of the vault, it may groove the inner table, sometimes giving the impression of convolitional markings.

If encephalography is done, one may find dilatation of the ventricle on the side of the lesion and perhaps attraction toward it because of cerebral atrophy caused by poor nutrition of the brain. If the lesion is in close contact with the ventricle, the latter may show a localized defect. It can even lie within the ventricle, as in cases involving the choroid plexus.

For angiography, it is important to inject both internal and even both external carotids to obtain a full mapping of the filling and draining vessels, especially if the lesion is situated near the mid-line or thinner surface of the brain. One frequently finds arteriovenous aneurysms irrigated from both sides.

The angiogram shows a formation of tortuous vessels in such close contact that it is impossible to separate them. Leading to this formation are many dilated feeding arteries. The draining veins are usually filled during the arterial phase of the injection. The simultaneous injection of the veins and arteries is characteristic of arteriovenous malformation. A glioblastoma multiforme, because of its vascularity, may be difficult to differentiate. There is always a shift to the opposite side in tumor cases, while in angiomatous malformation the shift, if any, is toward the lesion, except where there is associated intracerebral hematoma.

As an indication for angiography the author stresses focal epilepsy in young adults associated with localized atrophy, other than temporal, demonstrated by encephalography, since it cannot be certain that this atrophy is not due to a vascular malformation such as an arteriovenous aneurysm.

Fifteen roentgenograms.

MORTIMER R. CAMIEL, M.D.
Brooklyn, N.Y.

Intracranial Aneurysm: Surgical Diagnosis and Treatment. Rudolph Jaeger. S. Clin. North America 32: 1565-1583, December 1952.

Only since 1926 with the pioneer work of Moniz and Lima has visualization of intracranial aneurysms been possible. Pathologically, there are three types: arterial, arteriovenous, and carotid-cavernous aneurysms. The arterial aneurysm occurs at all ages and apparently has little relationship to syphilis, trauma, or arteriosclerosis. Those on the circle of Willis are congenital. The arteriovenous aneurysm is congenital and is characterized by lack of a capillary system between large arteries and the draining veins. The carotid-cavernous aneurysm represents a rupture of the intracavernous portion of the carotid artery as a result of trauma. The presence of bloody or xanthochromic

spinal fluid in the absence of trauma is the single best indication for cerebral arteriography, as it denotes the probable presence of an aneurysm.

Roentgenographically, an occasional aneurysm may be demonstrated on plain skull films as the result of calcification in the wall. In the author's series of 104 cases, 9 per cent showed calcification. Erosion of the skull near the carotid canal should lead one to suspect aneurysm, although it cannot be differentiated from erosion due to tumor except by arteriography.

The author performs arteriography with either Diodrast or Thorotrast, each having advantages and disadvantages. He uses the percutaneous technic with anteroposterior and lateral stereo views. When Thorotrast is used, 7 c.c. is adequate for the anteroposterior view and 6 c.c. for each lateral.

The only cure for these lesions is open exposure and ligation or promotion of fibrosis to strengthen the weakened wall of the vessel.

Thirteen roentgenograms: 5 photographs.

M. HARLAN JOHNSTON, M.D.
Jacksonville, Fla.

Angiographic Differentiation of Parasagittal and Falx Meningiomas. H. Haar and Th. Tiwisina. *Fortschr. a. d. Geb. d. Röntgenstrahlen* 77: 653-661, December 1952. (In German)

Meningiomas are considered the most satisfactory of the brain tumors for diagnosis by angiography and for surgical intervention. They comprise approximately 15 per cent of all brain tumors and occur most frequently in middle life. The purpose of the present paper is to point out the signs permitting a differentiation of meningiomas in the parasagittal region from those involving the falx.

The percutaneous method was used. Perabrodil M, 45 per cent, was injected into the common carotid artery, to insure distribution throughout the branches of both the internal and external carotids. This was often followed by injection of one or the other branch.

Meningiomas are richly vascularized and therefore are demonstrable as to location and size by the presence of the medium in the tumor. Visualization is often obtained to best advantage during the venous phase. Very often a vessel about the border of the tumor is of assistance in locating its size and position.

Parasagittal meningiomas in the anterior third of the brain displace the arteries (anterior cerebral) to the opposite side, where an angle is formed with the callosomarginal artery. The peak of the angle is at the knee of the corpus callosum, and the angle is bisected by the pericallosal artery. In meningiomas of the anterior and middle thirds, this angulation is characteristically shown in the postero-anterior projection. It is caused by pressure of the relatively free and movable arteries under the rigid margin of the falx. The falx is also displaced away from the tumor (positive falx sign). The blood supply to meningiomas of the anterior third of the brain is from the divisions of the external carotid in many cases.

The falx meningioma shows displacement of the arteries to the opposite side, but there is no positive falx sign in the postero-anterior projection. The lateral view shows depression and posterior displacement of the anterior cerebral and the anterior portion of the pericallosal arteries. In the phlebogram the vein of Galen is sometimes displaced in the occipital basilar direction.

Parasagittal meningiomas of the middle third of the brain show a positive falx sign and compression of the sylvian vessels as well as displacement of the anterior cerebral artery away from the tumor area. The falx meningioma does not show a positive falx sign or compression of the sylvian vessels.

In tumors of the posterior third there is only slight displacement of the anterior cerebral group, frequent compression of the sylvian vessels, but usually depression of the artery to the angular gyrus. There may be a slight positive falx sign. In the lateral view there is downward pressure on the middle cerebral group (posterior parietal angular gyrus and posterior temporal arteries). The falx meningioma in this region is often better demonstrated by vertebral angiography and shows upward displacement of the posterior cerebral artery. Meningiomas of the tentorium will also give this sign.

Tumors lying low in the middle third sometimes compress the carotid siphon and also the insular portion of the middle cerebral artery at its origin.

Identification of the above disturbances in position and relationship of arteries and veins plus opacification of the tumor and frequent demonstration of blood supply from both the internal and external carotid origins usually allow positive identification and diagnosis both as to size and position of these tumors.

Fourteen roentgenograms.

E. W. SPACKMAN, M.D.
Fort Worth, Texas

Supratentorial Tumors Among Children. Ross H. Miller, Winchell McK. Craig, and James W. Kernohan. *Arch. Neurol. & Psychiat.* 68: 797-814, December 1952.

A review of 518 verified brain tumors at the Mayo Clinic, occurring from birth through the age of fourteen years, disclosed 190 supratentorial tumors. These supratentorial tumors were reviewed as to type and location, signs and symptoms, roentgenologic findings and survival times.

There were 97 gliomas of various types, constituting 51 per cent of the total number of tumors. In most of these cases there was increased intracranial pressure with headache, vomiting, and visual disturbances. Roentgenographic examination of the skull revealed abnormalities in 59 patients. In only 19 were there abnormal deposits of calcium (9 astrocytomas, 4 ependymomas, 6 oligodendrogliomas), while 43 showed erosion of the sella turcica, and 36 separation of the suture lines.

Thirty-five craniopharyngiomas were found. Headache (88 per cent) and visual disturbances (82.9 per cent) were the common symptoms. In 28 cases (80 per cent) abnormal deposits of calcium were demonstrable either above or within the sella. In 29 (82.8 per cent) there were changes in the sella, and in 7 separation of the sutures. Seven patients with craniopharyngioma survived for more than five years after surgery (one for twenty-one years). It is interesting to note that 6 of the patients received irradiation therapy after surgery and 2 of these were alive at the time of the report (six months and twenty-one years).

Next in frequency were tumors of the pineal body. Fourteen were encountered, of which 9 were pinealomas, 4 were teratomas, and 1 was an astrocytoma of the pineal body. Roentgenograms of the skull showed abnormalities in 12 patients: erosion of the sella turcica

in 8, separation of the cranial sutures in 7, and abnormal calcium deposits in the area of the pineal body in 6.

Only 12 (6.3 per cent of the series) meningiomas were found. Eight of the 12 patients had changes in the skull roentgenograms. These consisted of abnormal deposits of calcium in the tumor in 4, separation of the cranial sutures in 2, and erosion of the sella turcica in 5. Meningiomas appear to be more malignant in children than in adults. Five patients (of the 12) were alive at the time of this report, but 2 of these were only six months postoperative.

Twelve sarcomas were found in this series: 5 fibroblastomas, 5 perivascular sarcomas, and 2 metastatic tumors. The skull roentgenograms were abnormal in 7 of the patients. Five had destructive skull lesions due to the tumor. One had erosion of the sella turcica and 1 had calcium deposits in a fibrosarcoma of the dura.

Nine of the tumors in this series were pituitary adenomas, of which 6 were of the chromophobe type. One was of the eosinophilic type and 2 were malignant adenomas. The average duration of symptoms was 22.7 months, with a range of two to fifty-four months. Eight of the 9 patients showed enlargement of the sella on roentgenograms of the skull. The one patient without sellar changes had had diabetes insipidus for thirty-six months.

Seven tumors were classed as arising from blood vessels. Two of these patients showed abnormal intracranial calcium deposits (1 of the Sturge-Weber syndrome pattern), while 1 showed separation of the sutures. Three epidermoids were included in the study, 1 of the frontal lobe and 2 of the skull. The former exhibited calcium deposits in the surrounding area; the latter produced "punched-out" defects. One patient had a tuberculoma in the area of the third ventricle.

Eight photomicrographs; 1 graph.

DEAN W. GEHEBER, M.D.
Baton Rouge, La.

Concerning the Roentgen Changes in the Septum Pellucidum. A. Ravelli. *Fortschr. a. d. Geb. d. Röntgenstrahlen* 77: 671-679, December 1952. (In German)

The septum pellucidum normally varies between 0.9 and 1.5 cm. in height and 0.2 and 0.3 cm. in breadth. Changes in the roentgen appearance may be produced by congenital or acquired factors, as congenital agenesis and cysts, which are demonstrated radiologically, conditions of early childhood causing atrophy associated with hydrocephalus, trauma due to penetrating wounds or operation.

Changes are demonstrable by encephalography or ventriculography. With agenesis, a single aerated space is seen, comprising both lateral ventricles. The so-called "communicating" cysts of the septum pellucidum are disclosed by communication of the cavum with the lateral ventricles, third ventricle, subarachnoid space, or cavum vergae. Occasionally a falx bone may simulate a closed cyst. The closed cavum may be difficult to differentiate from tumor (glioma, oligodendroglioma, astrocytoma, glioblastoma, etc.). The x-ray appearance is typical, showing a broadened gas-filled space between the two lateral ventricles. In association with alterations of the septum, defects of the corpus callosum may be demonstrated.

Fifteen roentgenograms; 2 photographs.

E. W. SPACKMAN, M.D.
Fort Worth, Texas

Importance of Early Surgical Treatment of Craniosynostosis. Review of 36 Cases Treated During the First Six Months of Life. Robert L. McLaurin and Donald D. Matson. *Pediatrics* 10: 637-652, December 1952.

The late signs of craniosynostosis such as mental retardation, visual impairment, and persistent headache indicate irreversible brain damage. Effective treatment of the condition demands prophylactic surgery and means that the operative approach must be made early, within the first few months. Cosmetic results in those treated early are also likely to be better. Surgical treatment is of no benefit in primary microcephaly and these patients need to be differentiated.

This report concerns 36 patients operated on during the first six months of life. The group comprised 19 instances of sagittal suture closure, 10 of coronal closure, 5 of multiple suture involvement, and 2 miscellaneous cases. Comparison of the results in these patients against those achieved in 84 patients operated on at a later age in the same clinic (Children's Medical Center, Boston), demonstrated the value of the earlier approach.

The operation of choice consisted of linear craniectomy parallel to the suture which was prematurely fused, with the insertion of polyethylene film over the bony margins to delay closure. Some patients operated upon before the routine use of the polyethylene film had to undergo a second operation because of closure of the craniectomy wound.

The poorest outlook in these various situations is found in the premature coronal and mixed coronal and sagittal closures. The patients with coronal closure usually have a greater disability and their surgical treatment is more complicated. They have a high incidence of associated congenital anomalies.

Experienced roentgenologic assistance is considered the single most important factor in differentiating primary microcephaly. Combined coronal and sagittal synostosis is particularly likely to be confused with microcephaly but, in the latter condition, films will show the suture lines to be present, though not as prominent as normal because of the lack of expanding force from within the skull.

Most of the patients reported here were operated upon by the age of three months. The youngest was only a week and a half old. With proper precautions and supportive therapy, surgery seems to be well tolerated and the complications are negligible.

Sixteen roentgenograms; 12 photographs; 2 tables.

JOHN F. RIESER, M.D.
Springfield, Ohio

Surgical Diagnosis in Cancer of the Head and Neck. Henry P. Royster. *S. Clin. North America* 32: 1599-1616, December 1952.

This paper deals primarily with the surgical diagnosis of cancer of the head and neck. Sometimes, however, tumors not visible clinically can be demonstrated roentgenologically if their presence is suspected. The essential abnormalities noted in the films are a disturbance of the air column in the mouth and respiratory system, and thickening, change of position, or loss of mobility of easily identifiable structures.

The key to the roentgen interpretation lies in a simple knowledge of the topographic anatomy of the area, for it is well shown in the delineation of air spaces in the anteroposterior and lateral films. On occasion, more

specialized technic may be solicited when the simple films do not satisfy, and the laminagraph is then used to "comb" a given area more accurately by serially focused beams at different depths.

In the nasopharynx the characteristic malignant lesion is the lymphoepithelioma, which projects into the epipharynx and reduces the air space. As it grows, it may invade the adjacent cranial bones.

The diseased soft palate may undergo a number of changes detectable on radiographic study. Although projections from its surface are common, changes in its position or motility form characteristic abnormalities. Paralysis from tumor, or dependency due to the heavy weight of a mass, is subject to demonstration, especially if the tissues are coated with Lipiodol.

At the root of the tongue in the vallecula, the crater of a tumor will entrap barium or Lipiodol and show on the films as well as fluoroscopically. Lesions situated on the epiglottis, posterior pharyngeal wall, and in the pyriform sinuses appear as projections into the air space of the oral cavity and respiratory passage. The position of the epiglottis may be changed so that it leans posteriorly. Malignant tumors usually are represented by irregular asymmetrical outlines, whereas benign lesions customarily are smooth and regular.

Tumors of the intrinsic larynx in various ways alter the air pattern as seen on the lateral film. Not only may projections into the lumen be clear-cut, but the delineation of the air space in the ventricles between the cords is often obliterated or made hazy by tumor growth.

Eleven illustrations, including 2 roentgenograms.

The Role of Radiology in the Management of Intra-ocular Foreign Bodies. R. S. Murray. J. Faculty Radiologists 4: 138-148, October 1952.

The technic for localization of intra-ocular foreign bodies as used at Moorfields Eye Hospital (London) during 1949-51 is reviewed. Sixty per cent of the bodies were in the coats of the globe behind the equator.

The great majority of the foreign bodies were removed by one of two methods, either by the anterior route, through an incision in the cornea, or by the posterior route, with reflection of a scleral flap over the foreign body. The latter procedure requires more precise localization than anterior removal.

The preliminary investigation determines whether or not there is an intra-orbital radiopaque foreign body, however minute. A postero-anterior occipito-oral and two lateral views are obtained using cardboard holders and a short exposure time. The involved side should be near the film on the lateral views; one film made centering on the outer canthus and the other slightly off-center. The patient should look straight ahead for all views. It is necessary to scrutinize the films carefully, with bright illumination.

Preliminary localization is then performed to identify gross extra-ocular position or establish an approximate intra-ocular location. Quadrant localization is always accurate, and frequently closer localization is possible by studying the axis change. Two methods are available for these determinations. One utilizes the previous films, relating the foreign body to the corneal outline anteriorly and the center of the globe, estimated as the center of the orbital bony ring, on the postero-anterior projection. In other cases a double-exposure lateral eye-moving projection is obtained, utilizing a head clamp. If one image is seen or only slight displacement is apparent, extra-ocular location is evident.

More precise localization is performed only if surgically indicated. The Bromley apparatus may be used if the patient is cooperative, if the lids can be opened enough so that the cornea can be seen, if the eye is not too irritable, and if the foreign body is not too small. The results should always be checked with the preliminary rough localization.

In cases unsuitable for the Bromley method, the limbal ring technic is used. A suitably sized limbal ring 9 to 12 mm. is accurately fixed by sutures to the adjacent conjunctiva. Postero-anterior and lateral views are then obtained with fixed forward vision. By reference to the ring, the foreign body may be plotted on the Bromley chart.

The foreign body position is related to the nearest scleral point at a distance from the limbus on the appropriate meridian passing through the center of the cornea. It may also be related to the three cardinal planes passing through the center of the cornea. In cases of non-magnetic bodies, where surgical removal is indicated, an opaque point of reference may be introduced surgically.

The results of the author's technic in 1,336 examinations carried out over a thirty-month period indicate its clinical reliability. Two hundred and five patients were found to have intra-orbital foreign bodies, and in 168 these were successfully localized. Localization is not feasible for multiple bodies.

Thirteen roentgenograms; 4 line drawings.

EDWARD E. TENNANT, M.D.
Jacksonville, N.C.

Cricopharyngeal Muscle Under Normal and Pathologic Conditions. Hans Brunner. Arch. Otolaryng. 56: 616-634, December 1952.

The two portions of the inferior constrictor muscle of the pharynx respond differently when the pressure in the hypopharynx is increased during the Valsalva maneuver. The oblique portion of the muscle becomes distended, while the circular portion, or the cricopharyngeal muscle, responds with contraction, forming a "hypopharyngeal bar." This is seen on the roentgenogram as a narrowing of the lumen in the region of the cricopharyngeal muscle.

The size of the defect produced by the contracted cricopharyngeal muscle permits some conclusions to be drawn concerning its excitability. Hypoexcitability was noticed in two cases of injury to the neck. A unilateral recurrent laryngeal nerve paralysis usually does not interfere with the contractibility of the cricopharyngeal muscle; in some cases it may cause hypoexcitability of the muscle. However, there is frequently difficulty in swallowing, as well as retention of barium in the hypopharynx. In functional disorders of the pharynx, there is frequently hyperexcitability of the cricopharyngeal muscle, associated with moderate and periodical dysphagia. In approximately 50 per cent of these disorders there is retention of barium in the hypopharynx. A prominent hypopharyngeal bar is frequently present in diseases of the pharynx or close to the pharynx. It is associated with retention of barium and usually with dysphagia. The finding of a prominent hypopharyngeal bar in carcinoma of the hypopharynx indicates that the tumor has not involved the cricopharyngeal muscle.

Seventeen roentgenograms.

HOWARD L. STEINBACH, M.D.
University of California

THE CHEST

Lymphatics of the Thorax: An Anatomic and Radiologic Study (Preliminary Report). Alejandro Celis and José Kuthy Porter. *Acta radiol.* 38: 461-470, December 1952.

This is a preliminary report of an attempt to find a means of rendering the lymphatics of the thorax opaque. For this purpose, an anatomic and radiologic study was carried out on 50 human cadavers.

While it is not possible to describe the lymph circulation in the lung as precisely as the circulation of the blood, some observations on the lymph flow are presented by way of introduction, and it is brought out that the lymph from both lungs, except for a small area at the left apex, drains *via* the right lymphatic duct into the right subclavian vein and not into the thoracic duct.

The authors used the following methods of study: (1) dissection of the thoracic duct; (2) injection of a dye into the duct followed by dissection; (3) opacification of the duct by injection of a contrast medium, both in the direction of the lymph flow and against it.

The radiologic examination showed the thoracic duct in most cases to consist of a single trunk without branches, situated either in front or to the left of the vertebral bodies, rising in an arch a few centimeters above the left subclavian vein and ending in the left internal jugular vein (1 case), the left subclavian (24 cases), or both (1 case). No communicating branches could be demonstrated between the thoracic duct and the pulmonary tissue or the lymph nodes at the pulmonary hilus. Nine variations from the normal radiological picture are briefly described.

The authors stress that this communication is of the nature of a preliminary report based only on the material and methods employed. No details of the radiologic technic are included.

Twelve roentgenograms; 1 drawing.

A. WILSON BROWN, M.D.
Shreveport, La.

The Use of Water Soluble Contrast Media for Bronchography. James V. Rogers, Jr., and H. Stephen Weens. *Ann. Surg.* 136: 971-977, December 1952.

Bronchography was done 16 times in 15 patients with a water-soluble medium, Ioduron B, which consists of a mixture of 50 per cent Ioduron (diethanolamine salt of diiodopyridon-N-acetic acid) and about 2.5 per cent water-soluble cellulose, to which small amounts of a wetting agent and preservatives are added. The medium is used in the same manner as iodized oil, but with special attention to securing complete local anesthesia. For the latter purpose, the authors used a 4 per cent cocaine solution (never more than 25 c.c.). The contrast medium is introduced under fluoroscopic guidance, and films are obtained with the patient upright.

The series reported here included a variety of pulmonary conditions. In 10 instances the bronchograms were of satisfactory diagnostic quality. In 4 patients the bronchial tree on the side under investigation was incompletely depicted because of inability to control coughing. Two examinations were complete failures. All patients were followed more than six months or until death, and in none were there any clinical or roentgen changes that could be attributed to the medium.

In order to facilitate comparison with iodized oil, the authors purposely refrained from the use of any special anesthetic procedure. It is their impression, from this small group of cases, that a greater amount of cocaine is necessary to control the cough reflex when a water-soluble medium is employed than with iodized oil, and that even then there is a greater tendency to coughing. For this reason, they have not considered it safe to examine both sides at single sitting.

In most instances the contrast medium disappeared from the bronchial tree in one to three hours, thus making possible re-examination within a relatively short time.

The general conclusion is reached that Ioduron B is well suited to use in those patients in whom bronchography may be confined to a limited number of segments, particularly in pathologic states in which partial bronchial obstruction enhances retention of oily media for considerable periods. In those patients, however, in whom a survey bronchogram of both lungs is required, iodized oils still possess advantages which outweigh their disadvantages.

An excellent discussion on the physiology of absorption of the medium, particularly of its viscosity-producing agent, is given.

Ten roentgenograms.

[Preliminary studies on the evaluation of Ioduron B for bronchography have been published by Hentel, Cohen, and Prandenstein (*Dis. of Chest* 21: 280-295, 1952. *Abst. in Radiology* 60: 110, 1953).]

JOSEPH P. TOMSULA, M.D.
Baton Rouge, La.

The Effect of Iodized Oil Bronchography on the Subsequent Course of Pulmonary Tuberculosis. A Review with a Study of 49 Cases. Vincent Marchese, Karl P. Klassen, and George M. Curtis. *Am. Rev. Tuberc.* 66: 699-721, December 1952.

There are numerous conflicting reports in the literature regarding the effect of iodized oil bronchography on patients with tuberculosis. The opinion that the administration of iodine to patients with pulmonary tuberculosis has an unfavorable effect upon the course of the disease has been held by many. It has also been stated that the introduction of iodized oil into the tracheobronchial tree may result in bronchogenic spread of the infection or lead to reactivation of an apparently healed focus of tuberculosis. The iodine in Lipiodol is chemically bound in the poppyseed oil, however, and is non-toxic and non-irritating to the bronchi unless it (the iodized oil) has deteriorated.

In the group of 49 patients selected for the present study, 34 had far advanced tuberculosis, 14 had moderately advanced, and 1 had minimal tuberculosis. It was found that bronchogenic spread of disease did not occur in patients who had shown a favorable roentgenographically demonstrated resistance-infection relationship during the period prior to bronchography. Bronchogenic spread of the disease can occur, however, in patients with sputum positive for tubercle bacilli and with roentgenographically demonstrable unstable and progressive lesions. On the other hand, positive sputum, pulmonary cavitation, bronchiectasis, or an unstable lesion does not necessarily indicate that bronchogenic spread will occur after Lipiodol bronchography. Adequate collapse therapy in the patients with unstable disease tends to prevent post-bronchographic spread of the disease. It is concluded that iodized oil bronchog-

raphy is a safe procedure in patients with controlled, stable, or regressive tuberculous lesions.

Two tables.

JOHN H. JUHL, M.D.
Minneapolis, Minn.

The Lateral Position in Chest Tomography. G. Simon. *J. Faculty Radiologists* 4: 77-88, October 1952.

For lateral chest tomography the standard technic used for the supine patient is applicable, with suitable adjustments of the exposure factors. The examination should be supervised by a radiologist, and the number of exposures should not exceed six.

Appreciation of the value of this examination is based upon a clear recognition of the normal anatomical structures. The mid-line cut demonstrates the sternum, vertebral column, and trachea. Proceeding to the left, the pulmonary artery and vein are identified, and at a distance of 2-4 cm. these structures can be seen terminating in their smaller branches. The apical division branch to the lower lobe arises as the pulmonary artery swings postero-inferiorly; the associated vein is slightly lower. The other lower lobe branches are seen in more lateral cuts. The main bronchus is easily identified as a well defined translucency.

Proceeding with cuts to the right, the apical lower lobe arterial branch is seen arising from the artery without the curving observed at this level in the left pulmonary artery. The three upper, the middle, and the lower branches are visualized as the cuts proceed laterally.

The lateral chest tomograph should be used only as a supplement to the more standard procedures of chest examination. It may be specifically helpful for the following purposes:

(1) *To Localize Tuberculous Lesions Prior to Surgery:* Identification of the fissures, vessels, and bronchi, even when they are displaced or distorted by pathologic processes, frequently will localize tuberculous cavities to a specific segment when routine studies fail because of atelectasis or contralateral conditions.

(2) *To Assess the Extent of a Lesion:* Although all disease will not be visualized on the tomograph, multi-segmental or multilobar disease which is not revealed on routine studies may sometimes be demonstrated by this method. This is of particular importance when evaluating candidates for partial resection.

(3) *To Determine the Pathology of a Lesion:* In some cases it is possible to obtain additional information which will assist in establishing a diagnosis. Encysted fluid may be distinguished from a pneumonic process. Massive fibrosis and a neoplasm may be differentiated.

(4) *To Clarify a Pulmonary Shadow Invisible or Indistinct in a Plain Lateral View:* Lateral tomography is of aid in investigation of lobar obstructive atelectasis, particularly with respect to the middle lobe; segmental atelectasis of the upper lobe, and space-occupying intrapulmonary lesions. The presence of postoperative pneumothorax or pleural adhesions and the degree of lobe re-expansion can be evaluated in spite of such contralateral conditions as thoracoplasty, pneumothorax, or extensive disease.

(5) *To Demonstrate the Main Branches of the Pulmonary Arteries:* Vessels, enlarged nodes, and arteriovenous malformations may be demonstrated.

(6) *To Supplement the Plain Lateral View in Evaluation of Mediastinal Tumors or Paratracheal Nodes:* Better definition of tumor margins allows a clearer

demonstration of their extent. Retrosternal masses not seen on routine studies have been observed. Cuts near the tracheal level may demonstrate paratracheal nodes.

Twenty-four roentgenograms.

EDWARD E. TENNANT, M.D.
Jacksonville, N. C.

Congenital Malformations of the Trachea, Bronchi and Lung. Paul H. Holinger, Kenneth C. Johnston, Victor N. Parchet, and Arnold A. Zimmermann. *Ann. Otol., Rhin. & Laryng.* 61: 1159-1180, December 1952.

This report covers 185 cases of various congenital abnormalities of the trachea, bronchi, and lungs obtained from clinical and autopsy material from St. Luke's Hospital, Children's Memorial Hospital, and the Research and Educational Hospitals of the University of Illinois, Chicago, from 1936 through 1951. The anomalies may become apparent at any age. In the first few weeks or months of life they often present serious respiratory emergencies.

The cases have been classified according to the following scheme, modified from Jordan (*Am Rev. Tuberc.* 40: 517, 1939):

- I. Anomalies of the trachea
 - A. Agenesis or atresia
 - B. Constriction or enlargement
 - C. Tracheal evaginations or outgrowths
 1. Tracheoceles, diverticula, and cysts
 2. Fistulas
 3. Tracheal lung
 - D. Abnormal bifurcation or deviation
 - E. Other anomalies of gross morphology
- II. Anomalies of the bronchi and lungs
 - A. Complete or essential agenesis or atresia
 - B. Constriction or enlargement
 1. Webs
 2. Compression from cardiovascular anomalies
 - C. Bronchial evaginations or outgrowths
 1. Bronchoceles, diverticula
 2. Congenital cysts
 3. Fistulas
 - D. Subnumery bronchi, lobes, fissures
 - E. Supernumery bronchi, lobes, fissures
 - F. Anomalous bronchial and lung tissue attached to some part of the respiratory system
 - G. Anomalous bronchial or lung tissue attached to tissues other than those of the respiratory system

Each type of anomaly is discussed, with examples from the authors' series. In summary, the authors state:

"The diagnosis of congenital malformations of the lower respiratory tract during life is made through the use of various services and the team work of the pediatrician, roentgenologist, bronchologist and thoracic surgeon. The history of obstetrical trauma or subsequent chest injury is important. From the physical findings one may differentiate a laryngeal anomaly from other obstructions to respiration by the character of the cry and the direct laryngoscopy. Physical examination of the chest is often the only method of interpretation of the x-ray film, when, for example, one must differentiate between an obstructive emphysema of one lung and an atelectasis of the opposite lung. A frequent

erroneous interpretation of this type was noted when infants were admitted with a single chest film, the report stressing the atelectasis of the relatively uninvolved side rather than the much more significant obstructive emphysema of the opposite side. Fluoroscopic study, inspiration and expiration films, the lateral view of the neck with the arms down and back to reveal the larynx, a barium swallow, bronchography, planography and angiocardiology all add significant information in special instances. Bronchoscopy without anesthesia is now an accepted diagnostic procedure in unusual respiratory conditions in infants. Limiting the duration of the procedure, the use of small instruments and the administration of oxygen through the scope during the examination all increase the margin of safety. Finally, exploratory thoracotomy in infants, now a feasible, well established procedure, increases the scope of diagnosis and adds therapeutic possibilities. . . . It is because of this phase of the problem that the clinical, particularly bronchoscopic, study of the malformations here presented was undertaken.

"As in all studies of congenital anomalies, the review of anomalies of the lower respiratory tract has shown a frequent association of anomalies of other organs and systems, as well as a frequent multiplicity of anomalies within the respiratory tract itself."

Twelve roentgenograms; 1 photograph.

STEPHEN N. TAGER, M.D.
Evansville, Ind.

Silent Nontuberculous Lesions of Chest Disclosed in Survey X-Ray Studies. J. Dewey Bisgard. *Arch. Surg.* 65: 109-111, July 1952.

Attention is directed to a very important by-product of the mass x-ray survey studies which are in progress throughout the country. It is likely that the benefits which will accrue to the non-tuberculous subject will equal or exceed those of the tuberculous subjects for whom the surveys are primarily conducted. The procedure provides an excellent opportunity to discover bronchogenic carcinoma, in some instances at a very early stage in its development. In no other internal concealed organ is there afforded an equal opportunity for making an early diagnosis of malignant disease. Benign silent tumors should be explored and usually resected, since (1) they may continue to grow and subsequently produce pressure symptoms; (2) since histological examination is necessary to exclude carcinoma; and (3) since certain of them have a propensity to undergo carcinomatous change.

Tuberculomas should be resected and examined not only to differentiate them with certainty from malignant disease but also to eliminate a possible source of dissemination.

Two tables.

BERT H. MALONE, M.D.
Brunswick, Ga.

Observations on the Progression of Minimal Pulmonary Tuberculosis. A Study Based on Findings in Army Rejectees. Herbert R. Edwards, David Reisner, and Marjorie Bellows. *Am. Rev. Tuberc.* 66: 666-679, December 1952.

A group of 4,079 draft rejectees with a roentgen diagnosis of minimal tuberculosis was studied by means of a single follow-up film taken approximately two years following the original examination. The original roent-

genogram and follow-up film were reviewed without any knowledge as to clinical course, age, race, etc. Two physicians read the films and, while there were some individual differences, several significant facts were determined on the basis of roentgen findings alone.

A classification of minimal tuberculous lesions based on their presumed pathologic character was used, and the lesions were grouped into the following three main categories: (a) exudative and exudative-productive; (b) productive and fibro-productive; (c) fibrocalcific and calcified. Progression rates were highest in the exudative and exudative-productive and lowest in the fibrocalcific and calcific types, with the rate intermediate in the productive and fibro-productive types. Higher progression rates were found in persons under twenty-five years of age than in those twenty-five years and older, and in the non-white races than in the white race.

It is preferable to separate minimal lesions into not more than three broad groups on the basis of roentgen characteristics. On the two extremes would be the "soft," exudative form and the "hard," stringy fibrotic and calcified types. The third group would include the lesions not definitely classifiable in either of the preceding groups and would represent an intermediate category of lesions.

Eight tables.

JOHN H. JUHL, M.D.
Minneapolis, Minn.

Bronchial Obstruction and Bronchiectasis Complicating Primary Tuberculous Infection. Janet B. Hardy, Donald F. Proctor, and James A. Turner. *J. Pediat.* 41: 740-755, December 1952.

Thirty-five patients believed to have bronchial obstruction secondary to primary tuberculous infection were studied. Twenty-nine patients were examined bronchoscopically, 11 of whom showed evidence of partial or complete bronchial occlusion. In one instance this appeared to be due to extrinsic pressure alone; in 10 instances it was the result of endobronchial disease, or a combination of endobronchial disease and extrinsic pressure. Five patients had evidence of acute infection, which was non-specific in type; in 11 there was evidence of chronic secondary pyogenic infection.

Bronchographic studies were done in 28 patients, and 20 of these were found to have bronchiectasis. This was sacular in 10 patients and tubular in 10. The bronchiectatic changes were equally distributed between all the pulmonary lobes, but showed preponderance in the anterolateral segments of the upper lobes, the apical segments of the lower lobes, and the right middle lobe.

The autopsy protocols of 186 children dying of tuberculosis were reviewed. Fifteen children were found to have bronchiectasis as a complication of primary tuberculous infection.

Twenty roentgenograms; 4 drawings.

HOWARD L. STEINBACH, M.D.
University of California

Hidden or Unsuspected Bronchiectasis in the Asthmatic. Richard H. Overholt and James H. Walker. *Ann. Otol., Rhin. & Laryng.* 61: 1198-1205, December 1952.

Bronchiectasis, hidden and unsuspected, is often present in the asthmatic patient and should always be suspected in bronchial asthma. Bronchial obstruction

is chiefly responsible for the clinical manifestations of bronchial asthma. Diminution of the bronchial lumen by partial or complete block leads to impairment of ventilation and gaseous interchange, followed by interference with the circulatory dynamics. Obstruction may be due to bronchospasm, bronchostenosis, foreign bodies, or nodes either compressing or perforating the bronchus. These factors may operate alone or in combination to produce bronchiectasis. The bronchial obstruction is usually segmental and may be partial or complete, with emphysematous changes or atelectasis. Hyperplastic and fibrotic lymph nodes resulting from repeated respiratory infection or pulmonary tuberculosis may encircle or compress the bronchi and produce obstruction.

Bronchiectasis is primarily a segmental disease, frequently bilateral, and may occupy any one of the 18 segments of the two lungs. The usual disease pattern includes involvement of the basal segments, the middle lobe, or the lingula. Any asthmatic patient with purulent sputum, hemoptysis, repeated respiratory infections, or clinical findings of localized râles should be suspected of having bronchiectasis.

At the Overholt Thoracic Clinic, from which this report comes, all patients undergo bronchoscopy during their period of investigation. In addition to removing the thick, tenacious, and adhesive secretions, one may at times localize a lesion by observing bronchostenosis, obstruction due to extrinsic pressure, or origin of purulent secretion from bronchiectatic segments.

An accurate appraisal demands bronchography, but this procedure is never attempted on a patient having moderate or serious respiratory distress. It is most important to record changes and findings observed during the fluoroscopic guidance of the contrast media into the bronchial tree.

Once the diagnosis of bronchiectasis is established, the treatment is surgical unless the disease is so extensive that it cannot be removed. The end-results in treating the bronchiectasis and bronchial asthma parallel the surgeon's ability to remove all of the diseased portions of the lung and to conserve all normal tissue.

During the past four years, 76 patients with severe bronchial asthma were treated at the Overholt Clinic. Bronchography was performed in 75 without ill effects, and bronchiectasis was demonstrated in 27. All were treated by exploratory thoracotomy, and in 26 the abnormal segments were removed. Two patients with infectious complications were not benefited. In 1 patient, the bronchiectasis was too extensive for removal. Twenty of the 26 patients were markedly improved, and only 7 of this number required bronchodilator drugs.

Seven roentgenograms; 2 photographs.

STEPHEN N. TAGER, M.D.
Evansville, Ind.

The Varieties of Infantile Pneumonia in the X-Ray Picture. P. Keller. *Fortschr. a. d. Geb. d. Röntgenstrahlen* 77: 684-690, December 1952. (In German)

Roentgen recognition of infantile pneumonic processes is important, as there may be few associated clinical symptoms or physical signs and the incidence is higher than has often been recognized.

The author considers the types of pneumonic involvement in the very young child of rather primitive form. He recognizes the following types: (a) interstitial pneumonia, (b) bronchial pneumonia (frequently with

miliary nodules), (c) hilar pneumonia with outward spread from the lung roots, (d) primary ascending pneumonia, (e) paravertebral "striped" pneumonia (with band-like involvement of a segment), (f) a more developed form designated by Wiskott as Grade 2, usually found in somewhat older children. This last is differentiated from the transitional form, which approaches croupous pneumonia.

Multiple views, especially those obtained in the oblique projections, were used to bring out typical appearances. Distribution was observed to be as follows: (1) right dorsal upper lobe segment, 42 cases; (2) left lower lobe apex, 13 cases; lateral segment of right middle lobe, 12 cases; (4) medial segment of right middle lobe, 7 cases; (5) apex of right lower lobe, 9 cases. In many instances more than one area of involvement was seen.

Predilection for involvement of the right dorsal segment of the upper lobe is due to anatomical factors. The child lies on the back, especially during sleep, and this position favors accumulation of septic secretion in the right dorsal upper lobe bronchus. The author believes that many pneumonias arise through aspiration of septic secretions from the nasopharynx.

Ten roentgenograms. E. W. SPACKMAN, M.D.
Fort Worth, Texas

The Diagnosis of Lung Cancer. Frank F. Allbritten, Jr., Thomas Nealon, John H. Gibbon, Jr., and John Y. Templeton, III. *S. Clin. North America* 32: 1657-1672, December 1952.

Of 451 consecutive cases of carcinoma of the lung reviewed by the authors, 29 per cent had obvious generalized metastases when they were first seen; 31 per cent showed generalized spread on exploration precluding operative removal; 21 per cent were resectable even though there was tumor outside the lung, and in only 19 per cent was the disease apparently still confined to the lung.

The average time between onset of symptoms and seeking medical advice was 2.8 months in this series. An average of five months elapsed between the time medical advice was sought and surgical treatment. These figures do not indicate the length of time cancer may have been present, as it is generally recognized that it may exist for long periods before producing symptoms.

A diagnosis of bronchogenic carcinoma was suggested in 86.6 per cent of these cases following roentgenographic studies. In only 2 per cent was there a roentgen report of no disease.

As with other types of cancer, early diagnosis is a prerequisite for cure. The authors believe that chest roentgenograms every six months in persons over forty would provide the best means of early diagnosis. Solitary pulmonary nodules, localized emphysema, any area of atelectasis, and minor differences in the root shadows of the two lungs are suggestive of neoplastic growth. [There is no mention in the article of the importance of recognition of recurrent pneumonia in the same pulmonary segment or pulmonary cavitation with irregular walls.]

Exploratory thoracotomy is a safe procedure and should be used more frequently, according to the authors.

Eleven roentgenograms; 2 photographs; 7 tables.

M. HARLAN JOHNSTON, M.D.
Jacksonville, Fla.

The Early Recognition of Bronchiogenic Carcinoma. Jim S. Jewitt. *Dis. of Chest* 22: 699-708, December 1952.

The author has observed 150 proved cases of bronchiogenic carcinoma during a period of four and a half years. Exploratory thoracotomy was done on 35 per cent of the entire group, and only 12 per cent of the cases were suitable for resection. An analysis of the case histories revealed an average delay of 10.5 months between the onset of symptoms and the establishment of a correct diagnosis. The physician was responsible for an average delay of 6.4 months, and the patient for 4.1 months.

The author believes that earlier diagnosis is possible, since there are significant early symptoms and radiographic abnormalities in a high percentage of cases. He has tabulated the symptoms, radiographic, bronchoscopic, and cytologic findings depending upon the location of the tumor. His tabulation of the roentgenographic findings, most of them early, is as follows:

Main stem or lobar bronchi

1. Unilateral hilar nodularity
2. Localized emphysema on expiration
3. Persistent or recurring infiltration (pneumonitis)

Segmental bronchi

1. Segmental infiltration and/or atelectasis
2. Lung abscess distal to bronchial obstruction
3. Filling defect on bronchogram

Mid-lung peripheral tumors

1. Solitary pulmonary mass or "coin" lesion (may be detected if 3 mm. in diameter)

Peripheral invasive tumors

1. Peripheral mass
2. May not be visible until late

Failure on the part of the physician to recognize the lesion early is due (1) to minimizing the clinical picture, (2) to failure to obtain a chest roentgenogram, (3) to misinterpreting or overlooking significant roentgenographic departures from the normal.

Twelve roentgenograms; 2 tables.

HENRY K. TAYLOR, M.D.
New York, N. Y.

The Diagnosis of Mediastinal Tumors. W. Emory Burnett, George P. Rosemond, and Robert M. Bucher. *S. Clin. North America* 32: 1673-1694, December 1952.

The authors list two pitfalls in consideration of mediastinal tumors, namely, failure to diagnose the lesion and failure to remove it promptly. They reviewed 79 cases of mediastinal tumors, 65 of which were operated upon and followed for at least two years.

Roentgenographic examination is much more informative than all other diagnostic aids. Routine studies should include fluoroscopy, with study of the esophagus. Additional information may be gained by planigraphy, bronchography, and angiography. A most valuable diagnostic clue is the position of the lesion in the mediastinum, as demonstrated on a lateral chest film. The anterior mediastinum harbors teratoids, pericardial cysts, bronchogenic cysts, and lesions of the lymphatic tissues, including the thymus. The posterior mediastinum contains the neurogenic tumors and gastrogenic cysts. The superior mediastinum encompasses lesions of the thyroid, aorta, and lymphatic tissues. The authors suggest that an indefinite border is most often associated with benign

lesions, while a nodular or bosselated border suggests malignant growth. Bone erosion is of great help in the differential diagnosis of mediastinal tumors situated posteriorly.

It is of particular interest that 7 of 18 neurogenic tumors were classified as malignant. Among the 65 operated cases, there were 18 malignant growths, of which 11 were excised.

Pericardial cysts need not be removed, with the exception of lymphomas. All other mediastinal tumors should be removed because of their potential malignancy or possible complications with increase in size.

Twenty-three roentgenograms; 5 photographs; 1 table; 1 drawing. M. HARLAN JOHNSTON, M.D.
Jacksonville, Fla.

Erythema Nodosum with Bilateral Hilar Gland Enlargement: A Clinical Syndrome. Lasar Dunner and R. Hermon. *Brit. M. J.* 2: 1078-1080, Nov. 15, 1952.

This is a report of 6 cases of erythema nodosum in which chest radiography revealed bilateral hilar adenopathy. In each of the cases it was felt that the adenopathy was a manifestation of the primary disease. The patients were all relatively young women (the oldest thirty-seven). Tuberculosis, bacterial and virus infections, and sarcoidosis were felt to be excluded, and none of the patients had received sulfonamide or other chemical agents. In 3 instances the hilar adenopathy cleared spontaneously in one to seven months.

The authors believe that the routine practice of chest roentgenography in patients with erythema nodosum would lead to recognition of more cases of the type reported. An initial negative chest study should be followed in several weeks by another study.

The condition may warrant acceptance as a clinical syndrome.

Five roentgenograms.

JOSEPH P. TOMSULA, M.D.
Baton Rouge, La.

The Clinical Diagnosis of Anomalous Pulmonary Venous Drainage. H. A. Snellen and F. H. Albers. *Circulation* 6: 801-816, December 1952.

Anomalies of pulmonary venous return may be partial or total and vary as to the site of drainage. The authors report 1 case of partial and 4 cases of total abnormal return.

In the partial case a large vessel with tributaries coming from the entire lung could be seen in the lower portion of the right lung field. On angiocardiology it appeared to empty all the blood from the right lung into the inferior vena cava. The resulting recirculation of blood through the right side of the heart naturally put a strain on the right ventricle and was causing dyspnea on exertion. Both the right atrium and ventricle were enlarged.

In the presence of total abnormal drainage, some additional anomaly is necessary to sustain life and usually takes the form of an atrial septal defect. The size of the defect probably determines the length of life, since some patients with this anomaly die in infancy while others may live a relatively normal time. In the 4 cases recorded here the plain films showed a constant and characteristic picture. There is a rounded bulging of the superior mediastinum (dilated superior vena cava carrying blood from both pulmonary and systemic veins), with more prominence on the right. The right auricle bulges and the right ventricle is somewhat en-

larged, but the left auricle, left ventricle, and aorta are normal or small. The appearance of the cardiovascular silhouette in the postero-anterior view is best described as "figure-8."

Catheterization, angiocardiology, and in one case thoracotomy established the diagnosis. Associated anomalies besides the necessary atrial septal defects included situs inversus abdominis, infundibular stenosis, and a possible pulmonary stenosis.

Anastomosis of the superior vena cava with the left atrium is suggested if surgery appears to be indicated, but no procedure was carried out in any of the authors' cases.

Twelve roentgenograms; 5 drawings; 5 tables.

ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Cardiac Mensuration by Roentgenologic Methods.

Theodore F. Hilbisch and Russell H. Morgan. *Am. J. M. Sc.* 224: 586-596, November 1952.

In an effort to determine the average values and the ranges of the various cardiac measurements in normal individuals, the authors examined by teleroentgenography 500 persons who came to Johns Hopkins Hospital with no history of heart disease. The ages ranged from two months to fifty years. Approximately 100 cases were studied in each decade. Measurements were made of the transverse, long, and broad diameters of the frontal plane area of the heart, and these were tabulated as average values and normal ranges.

The data presented indicate that normal ranges of the various cardiac dimensions are quite large and overlap the pathological ranges to a considerable degree. Furthermore, these normal cardiac ranges are not amenable to great reduction by statistical methods of correlation with physical factors in most cases.

The authors believe that cardiac mensuration should be reduced to the simplest possible terms and therefore recommend that the frontal plane area be studied and correlated with the transverse thoracic diameter. It is further suggested that a note be included in the patient's history to indicate whether or not the values fell within the normal range of this dimension. If so, an additional statement should be made to indicate that this does not necessarily mean that the heart is not enlarged, since the normal and pathological ranges of heart size overlap to a considerable degree. Finally, it must be recognized that all cardiac measurements assume significance only when it is possible to compare them with those made at previous or subsequent examinations. Only then can an estimation be made of the progression or regression of the cardiac disease.

Two diagrams; two tables.

DANIEL WILNER, M.D.
Atlantic City, N. J.

Abscesses of Myocardium Due to Suppurative Mediastinal Dermoid: Angiocardigraphic and Pathologic Study. Sidney B. Rosenbluth, Israel Steinberg, and Charles T. Dotter. *Ann. Int. Med.* 37: 1064-1077, November 1952.

A case of myocardial abscesses due to direct extension from a dermoid cyst is reported. In most instances cardiac abscesses occur as part of a more widespread systemic disease.

The initial chest film in the authors' patient revealed a circumscribed shadow in the region of the pulmonary

artery, assumed to represent pulmonary artery enlargement due to cardiac disease. Four years later the same shadow was much larger, and an electrocardiogram suggested anteroseptal myocardial infarction. Angiocardigraphic examination revealed a large non-vascular mediastinal mass related to and displacing the heart. A malignant mediastinal tumor, with myocardial invasion, was suspected. The patient died very suddenly four days later. An autopsy revealed an infected dermoid cyst of the anterior mediastinum with a sinus tract communicating with an abscess in the myocardium. There was also an acute suppurative myocarditis.

The clinical course in this case followed the usual pattern of infected mediastinal dermoids with the exception of cardiac involvement and sudden death. Earlier recognition and surgical removal might have prevented the fatal outcome.

Seven roentgenograms; 5 photographs and photomicrographs; 1 electrocardiogram.

R. H. LEAMING, M.D.
Memorial Center, N. Y.

Recurrent Tuberculous Pericarditis. Ray C. Janovsky, John F. Boettner, H. Scott VanOrdstrand, and Donald B. Effler. *Ann. Int. Med.* 37: 1268-1274, December 1952.

Shock and pain are seldom considered to be prominent manifestations of tuberculous pericarditis. The onset of the disease is usually insidious, and pain, when present, has most often been reported as a dull ache vaguely localized to the chest. The case presented here is unusual in that it was characterized by repeated attacks of agonizing precordial pain. Its tuberculous nature was proved by biopsy.

Uncomplicated primary tuberculous pericarditis is a rare condition and may be indistinguishable clinically from so-called acute benign pericarditis. Important features of the latter are said to be its occurrence in healthy young adults, its appearance following upper respiratory tract infections, electrocardiographic changes of acute pericarditis reverting to normal within one to six weeks, and frequently recurrent attacks. All of the above findings were conspicuously present in the authors' case, which would seem to indicate that bacteriologic evidence may be the sole means of differentiating the two conditions. The advisability of pericardial biopsy should be considered in all cases of pericarditis of obscure etiology running a protracted course.

Two roentgenograms; a series of electrocardiograms; 1 photomicrograph.

STEPHEN N. TAGER, M.D.
Evansville, Ind.

Mitral Stenosis with Exertional Cyanosis and Pulmonary Hemosiderosis. James A. Wier, Amo J. Piccoli, David G. Greene, and Clayton W. Greene. *Circulation* 6: 868-873, December 1952.

The authors report a case of mitral stenosis in which exertional cyanosis was shown to be due primarily to stasis of the circulation as a result of the extremely small mitral orifice. The presence of small distended venules observed in the areas of most severe cyanosis may have been a contributing factor. In addition, the patient had a marked pulmonary hemosiderosis manifest on the chest film by diffuse, small, evenly distributed nodulations and a few irregular areas of calcification. This

however, was held to have had a relatively minor adverse effect on pulmonary function.

Three roentgenograms; 2 photomicrographs.

ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Prominence of the Left Mid-Cardiac Segment in Thyrotoxicosis as Visualized by Roentgen Studies. Samuel U. Greenberg, J. A. Rosenkrantz, and Samuel L. Beranbaum. *Am. J. M. Sc.* 224: 559-564, November 1952.

The authors investigated 106 cases of thyrotoxicosis and found that the left mid-cardiac segment was prominent in 67 per cent; in 42 per cent of the patients the enlargement was pronounced. There were no other apparent cardiovascular complications.

The mechanism which causes the increased prominence of this segment has not been established. It has been stated that the rate of the blood circulation and cardiac minute-volume output are increased in thyrotoxicosis to satisfy an augmented demand for and consumption of oxygen. The increase in the left mid-cardiac segment might represent dilatation of the pulmonary artery in order to satisfy oxygen requirements, as demonstrated by Parkinson and Cookson. With increased cardiac output, the right ventricle works against a constant pressure in the pulmonary circuit. Consequently, intra-arterial pressure increases and the pulmonary artery dilates (Menard and Hurxthal). It has been suggested that the peripheral capillary dilatation plus the increased vascularity of the thyroid gland may act virtually like an arteriovenous shunt, leading to enlargement of the right ventricular outflow tract and thus to dilatation of the pulmonary artery.

Four roentgenograms. DANIEL WILNER, M.D.
Atlantic City, N. J.

THE DIGESTIVE SYSTEM

Problems in Differential Diagnosis of Lesions of the Lower Portion of the Esophagus and the Cardia. Herman J. Moersch. *Ann. Otol., Rhin. & Laryng.* 61: 976-986, December 1952.

The lower portion of the esophagus and the cardia offer a great variety of organic, developmental, and psychomatic disturbances, often presenting difficult diagnostic problems.

Cardiospasm may occasionally be mimicked by other types of esophageal disease. It varies from slight obstruction at the cardia with minimal dilatation of the esophagus to marked obstruction with huge esophageal dilatation and angulation as shown radiographically. In cases of doubt as to the diagnosis, esophagoscopy should be performed. If, however, extreme angulation occurs in the lower end of the esophagus, some difficulty may be experienced in passing the esophagoscope through the cardia into the stomach, and the correctness of the diagnosis may be questionable. In such cases, an intramuscular injection of mechohyl may prove decisive. This will induce tetanic contraction of the esophagus with severe substernal distress not observed in any other type of esophageal disease.

Diffuse spasm of the lower third of the esophagus is frequently confused with cardiospasm. Roentgenograms show, in addition to the spasm, slight dilatation of the upper esophagus. The esophagoscopy findings vary according to whether the examination is performed under topical or general anesthesia. Under

general anesthesia, only a mild degree of esophagitis may be encountered. With topical anesthesia, the lower third of the esophagus will be found closed, and the obstruction must be overcome gradually by applying gentle pressure to the instrument as it is advanced.

Carcinoma of the lower end of the esophagus and cardia may offer a great deal of difficulty in diagnosis, especially in those cases originating in the cardia and infiltrating under the esophageal mucosa, producing obstruction without evidence of ulceration or tumefaction. Roentgen examination alone is not reliable for the diagnosis. Biopsy, along with cytologic study of secretions or smears from the site of obstruction, should be diagnostic in a high percentage of cases.

Benign tumors of the esophagus are rare and confusing. Both mucosal and intramural extramucosal tumors may present a clinical history and roentgenologic appearance suggestive of cardiospasm.

Hiatal hernia is frequently a source of diagnostic difficulty. In the presence of ulceration, it may stimulate secondary spasm of the esophagus. The problem is complicated by the fact that hiatal hernia may not be primary but may be a secondary manifestation of such conditions as carcinoma, scleroderma, esophagitis, or cicatricial stricture of the esophagus. Finally, foreign bodies may become lodged in a hiatal hernia, or other diseases may develop and greatly alter the findings.

Congenital anomalies of the lower part of the esophagus, esophageal varices, esophagitis, tuberculosis, fungous diseases, and post-traumatic changes of the esophagus may give rise to clinical symptoms similar to those of cardiospasm. It may be difficult to distinguish them not only from cardiospasm but also from one another.

A number of illustrative cases are reported.

Eleven roentgenograms; 1 photograph.

STEPHEN N. TAGER, M.D.
Evansville, Ind.

Importance of Functional Disturbances in the Recognition of Disease in the Walls of the Digestive Tract. H. J. Sielaff. *Fortschr. a. d. Geb. d. Röntgenstrahlen* 77: 705-712, December 1952. (In German)

The importance of recognizing the association of functional disorders with early organic and neurovegetative changes is frequently overlooked. Four brief case summaries are given illustrating this association. Caution should be observed in any case showing what appears to be merely functional change in the esophagus, especially if symptoms reappear after a period of time. In the author's experience, there have been many instances of unsuspected carcinoma diagnosed at a later date, in which careful study at the earlier examination might have demonstrated the lesion.

The functional phase is brought about by disturbance of the vagus reflex, which normally relaxes the cardia during the act of swallowing. Every patient with apparent functional disturbance should be thoroughly studied for such underlying organic lesions as esophagitis, other inflammatory and infiltrative conditions, and particularly early carcinoma of the middle third. Less frequent causes of the phenomenon are diverticula of the esophagus (either traction or pulsion) and such abdominal conditions as ulcer, inflammatory lesions, and neoplasms. Some authors go so far as to include endocrine and central nervous conditions.

Cardiospasm may be very refractory to treatment, and the author believes that particular attention to a possible underlying cause, especially early cancer, may

allow operative intervention before metastasis occurs.
Six roentgenograms; 2 graphs.

E. W. SPACKMAN, M.D.
Fort Worth, Texas

Esophageal Contraction and Cardiac Pain. William Evans. *Lancet* 2: 1091-1097, Dec. 6, 1952.

The author describes an abnormal radiological sign which he designates as esophageal arrhythmia. This is best observed by following the progress of the barium meal fluoroscopically. The first portion of the meal is seen to halt, often momentarily, at the diaphragmatic opening, and some of it may pass into the stomach. When the next portion of the meal arrives, it is again held up, and each additional supply of barium distends the lower end of the esophagus. As the act of swallowing proceeds, the air above presses on the column of barium below and causes the tube to swell still more, but the esophageal trap holds firm, and the bulk of the meal fails to enter the stomach. The next notable event is a sharp recoil of the meal, so that it is suddenly jettisoned upward into the gullet, whose lumen resumes its customary narrow caliber for a brief period. This series of events may be re-enacted several times before the barium is ultimately discharged piecemeal into the stomach.

Having first observed this phenomenon in a patient with the cardiac-like pain characteristic of coronary disease but with a normal electrocardiogram, the author decided to make a further study of its occurrence. The investigation thus initiated covered some fifteen years, during which several groups of patients were examined. Among 700 healthy subjects esophageal arrhythmia was observed in only 7 (1 per cent). It was present in 5 (2.5 per cent) of 200 persons with painless heart disease of various types and in 25 (5.0 per cent) of 500 patients in whom cardiac pain was associated with an abnormal electrocardiogram due to cardiac infarction. In marked contrast to the low incidence in these groups was the occurrence of the sign in 133 (40 per cent) of 332 patients with chest pain subjectively characteristic of cardiac pain but in whom electrocardiograms failed to confirm the presence of coronary arterial disease.

This finding is accepted as meaning that when a patient with cardiac-like pain presents a physiological electrocardiogram, even after exercise, and at the same time shows esophageal arrhythmia, the pain has a dyspeptic source. This assumption was further confirmed by follow-up studies. In only 5 of the 332 cases was an abnormal electrocardiogram subsequently obtained. There were 14 deaths in this series, of which only 1 was attributable to heart failure, while of 1,000 patients with true cardiac pain followed over the same observation period, 184 died from cardiac infarction.

The cardiac pain is not believed to be due to the esophageal spasm. Though no deliberate search was made for gastrointestinal lesions in the absence of signs and symptoms pointing to their presence, 18 patients were found during the period of observation to have some form of alimentary tract disease.

It is felt that the radiological sign of esophageal arrhythmia in patients with cardiac-like pain in the presence of normal electrocardiographic findings will aid in distinguishing a group of patients who otherwise might be unnecessarily subjected to the restrictions incident to a diagnosis of coronary arterial disease.

Four illustrations, including 2 roentgenograms; 4 tables.

Stenosis of the Esophagus in Benign Mucous Membrane Pemphigus. Edward B. Benedict and Walter F. Lever. *Ann. Otol., Rhin. & Laryng.* 61: 1120-1133, December 1952.

Benign mucous membrane pemphigus is a disease entity unrelated to pemphigus vulgaris, pemphigus foliaceus, or pemphigus vegetans. It differs from these three forms of true pemphigus in clinical appearance, course, and histology. The characteristic feature is the presence of bullous lesions and erosions on the mucous membranes, with subsequent scarring. The conjunctivae are most frequently involved, with oral mucosa next in frequency. Four cases with esophageal involvement are here reported.

The esophageal lesions consist in diffuse inflammation of the mucosa and submucosa with scarring leading to soft adhesions having the appearance of webs. Three of the authors' patients had corneal lesions as well. All experienced dysphagia. In one case no evidence of stricture was demonstrated roentgenographically, though esophagoscopy showed a web-like adhesion in the cricopharyngeal region. In the other 3 cases roentgenograms showed esophageal strictures which proved to be due to adhesions of the characteristic web-like form.

Recognition of esophageal involvement in benign mucous membrane pemphigus is important, for the soft adhesions, as present in the early stage, can easily be divulsed, while in their later stage they may resist treatment by bouginage. Any patient with benign mucous membrane pemphigus complaining of dysphagia should therefore be given a roentgen examination of the esophagus. Since webs may not be demonstrable roentgenologically, esophagoscopy should be performed, regardless of the x-ray findings.

Two roentgenograms; 1 photograph; 2 drawings.

STEPHEN N. TAGER, M.D.
Evansville, Ind.

Minor Degrees of Partial Thoracic Stomach in Childhood. I. J. Carré, R. Astley, and J. M. Smellie. *Lancet* 2: 1150-1153, Dec. 13, 1952.

The present report, which the authors designate as "preliminary," is based upon 112 cases of short esophagus and minor degrees of partial thoracic stomach in children. In none did the thoracic portion exceed 15 per cent of the entire stomach. Vomiting was an invariable symptom, dating from birth or the early neonatal period in 90 per cent of the patients.

Clinically, three groups of cases were observed. In one the symptoms ceased or very largely abated by the age of two years, and subsequent complications were not observed. In a second group there was no significant improvement till the age of four or later, and even then occasional relapses occurred, though eventually all symptoms usually disappeared. The third group was complicated by esophageal stricture, and in these patients dysphagia was the predominant feature.

Roentgen examination revealed the partially thoracic stomach and gastroesophageal reflux. The course of the esophagus was normal, ending above the diaphragm, at the highest point of a small gastric pouch. In the majority of cases, there was a constriction representing the cardia, and below this the lumen was expanded, often asymmetrically with respect to the axis of the esophagus. The gastroesophageal angle was reduced, and the gastric mucosal folds converged upward toward the hiatus, which was wider than usual. In the thoracic portion of the stomach, they appeared as rather coarse

vertical rugae, although sometimes irregular folds were also present. At the constriction representing the cardia, they were gathered together, to diverge above as finer esophageal folds. Sometimes complete filling of the thoracic portion was very transitory, and for that reason careful fluoroscopy is of importance. When a complicating stricture was present, the exact point of transition from esophagus to stomach was often ill-defined.

After symptomatic improvement, the partial thoracic stomach persisted unchanged, although reduction or absence of reflux made its demonstration more difficult. Occasionally barium ceased to regurgitate into the esophagus, although it still passed up into the thoracic part of the stomach; more often an effective closure mechanism seemed to develop at the level of the diaphragm, thus preventing or reducing the amount of barium passing into the thorax. When a stricture had occurred, a stationary state seemed more common than progression. In 2 children treated by dilatation all x-ray evidence of the stricture disappeared.

The relatively short and benign course in three-fourths of the authors' series, the gradual symptomatic cure in many of the others, and the low incidence of esophageal stricture are contrary to the impression conveyed by the literature, in which complicated cases predominate.

Six roentgenograms.

Early Roentgen Diagnosis in Massive Bleeding from the Upper Gastrointestinal Tract. I. Clinical Evaluation of Safety and Reliability of the Method in 123 Patients. Norman Zamcheck, Thomas P. Cotter, Simon E. Hershorn, Thomas C. Chalmers, Max Ritvo, and Franklin W. White. *Am. J. Med.* 13: 713-724, December 1952.

Emergency roentgen examination of the gastrointestinal tract was performed in 123 patients with severe bleeding. The patients were divided into two groups. The first 52 (Group A) received special attention not usually available to ward patients. They were attended by a large group of radiologists, surgeons, and ward physicians. Decisions regarding management were made on consultation of the several specialists, and the patients were carefully followed after examination, by various members of the team. The remaining 71 patients (Group B) were managed in a more routine manner, with the idea of determining the accuracy and safety of the emergency roentgen method when applied without the special supervision afforded in the earlier group. All patients had gross hematemesis or tarry stools, or both, and were considered medical emergencies. Many were admitted in shock. Ninety-three were examined within three days after admission.

In the beginning, *i.e.*, in Group A, an attempt was made to adjust the examination to the clinical condition. The patient was permitted a minimum of active motion. He was lifted on and off the examining table if necessary. Manual pressure was applied to the abdomen in 44 cases. The pressure cone was used in only 5. Fluoroscopy with spot films and routine roentgenography were performed. The relative safety of the procedure having become apparent, a complete roentgenoscopic examination was done, including use of the pressure cone, in 38 patients of Group B; in 13 instances the examination was complete except for the application of pressure and/or use of the erect position. In 16 patients no record was made of the completeness

of the examination, though it is assumed to have been relatively complete. In the remaining 4 cases the examination was unsatisfactory.

Follow-up studies were done by one or more of the following procedures: roentgen examination, gastroscopy, esophagoscopy, and gross and microscopic examination of lesions seen at operation or postmortem. The initial roentgen diagnosis proved to be correct in 92 instances. Diagnostic errors were made initially in 14 cases, including 7 of gastritis subsequently discovered. In 6 other patients follow-up studies confirmed the original observations but revealed additional lesions not previously diagnosed. In 11 instances no satisfactory roentgen diagnosis was made. A comparison of the cases with complete and incomplete examination indicated that the chances of error or of achieving no satisfactory diagnosis were approximately twice as great in the latter group.

One hundred and one of the 123 patients failed to show any evidence of continued or renewed hemorrhage following the emergency roentgen examination. Twelve patients bled severely after the examination, 3 in Group A and 9 in Group B. Eight of these were actively bleeding at the time of the examination. In no instance was it possible to establish or disprove a causal relationship between the roentgen procedure and the subsequent bleeding. Clearly, however, no deaths could be attributed to the examination. Greater safety could have been ensured by postponing examination until all evidence of bleeding had subsided, as was commonly done in Group A. Strict adherence to this rule, however, would exclude from examination those patients most urgently requiring accurate diagnosis, *i.e.*, those most likely to need emergency surgery.

It is concluded that emergency roentgen examination of the gastrointestinal tract may be performed with reliability, and that more extensive examinations may be made with greater safety than was formerly believed possible. The use of early repeat roentgen study is recommended.

Fourteen tables.

Gastrointestinal Changes in Pneumoperitoneum. I. D. Bobrowitz, Frederick Elias, and Jacob Ochs. *Am. Rev. Tuberc.* 66: 750-757, December 1952.

In order to determine the effect of pneumoperitoneum on the gastrointestinal tract, a series of 37 unselected patients approved for that procedure were studied. Roentgenographic examinations of the upper gastrointestinal tract were made before induction of pneumoperitoneum and again six weeks and six to eight months afterward.

Some or all of the following typical anatomic changes were observed in most of the patients studied: elongation and narrowing of the cardiac portion of the stomach, widening or dilatation of the fundus, anterior displacement and a drop of the stomach. The changes are due to the pressure of the air on the stomach, producing lengthening and narrowing, resulting in a drop. Since most of the air collects beneath the diaphragm, it also tends to push the abdominal viscera downward.

There was little correlation between the gastrointestinal symptoms and the anatomic alteration resulting from pneumoperitoneum. Most of the anatomic changes occurred early, with little change after six weeks, indicating early adjustment to the air.

Six roentgenograms.

JOHN H. JUHL, M.D.
Minneapolis, Minn.

Clinical Appraisal of Gastrointestinal Antispasmodics. Gordon McHardy and Donovan C. Browne. *South. M. J.* 45: 1139-1144, December 1952.

The authors studied the effects of Bentyl hydrochloride, Banthine bromide, and Prantal on the gastrointestinal tract in 75 persons, 25 for each preparation. Two other groups of 25 each received, respectively, atropine and a placebo, for purposes of comparison. The observations included a radiologic study of barium motility, gastroscopic appraisal of tonicity, and clinical symptomatic response.

The radiologists were kept in ignorance of the scheme and what material had been administered, so that conclusions might be rendered without knowledge of which preparation was used. Complete control was not possible, however, as patients receiving atropine or Banthine displayed the side-effects of mydriasis and xerostomia. Bentyl gave no clue; Prantal rarely produced recognizable side effects. Gastric peristalsis was estimated as normal, hyperactive, hypoactive, and non-effective. All subjects were normal, without demonstrable gastrointestinal disease or dysfunction.

All three of the antispasmodics under investigation produced a significant decrease in motility of the barium meal as compared to the placebo and to atropine. The most marked delay in each instance seemed to be in gastric emptying. On reviewing the films, however, the authors were more impressed with the appearance of gastric atonicity than with radiologic evidence of marked influence on pylorospasm.

Another group studied consisted of 80 selected patients with radiologic and symptomatic hyperperistalsis who were segregated into four groups and re-examined with the various drugs. Control ileocecal transit time in each instance was less than ninety minutes with an average of three defecations during this interval. After Bentyl, Banthine, and Prantal there was an average of one defecation in the first 120 minutes with no appreciable symptomatic difference in the three drug groups. The atropine group, however, averaged four defecations in the evaluative 120-minute period.

Thirty patients with well established antral or pylorospasm were also studied fluoroscopically following parenteral administration of Bentyl, Banthine, and Prantal and evaluated in terms of no influence, amelioration, or complete subsidence. Complete relief of the pylorospasm was obtained in 61 per cent of those receiving Bentyl, 74 per cent of those receiving Banthine, and 70 per cent of those receiving Prantal. The figure for atropine was 39 per cent and for the placebos 15 per cent.

The conclusions drawn from these studies are that Bentyl, Banthine, and Prantal are antispasmodics of comparable efficiency, with the suggestion that Bentyl has no untoward influence on the esophagus and less antisecretory effect than do Banthine and Prantal. The absence of significant side-effects with Bentyl permits more general use when secretory inhibition is not of the first import. All three drugs were considered more effective than atropine.

Five roentgenograms; 1 graph.

JOHN M. KOHL, M.D.
Jefferson Hospital

Prolapse Gastric Mucosa. Its Diagnosis and Significance. William Tom Arnold. *Texas State J. Med.* 48: 758-762, November 1952.

Prolapse of the gastric mucosa is encountered

principally in the fourth, fifth, and sixth decades. Epigastric pain and digestive symptoms including nausea, indigestion and loss of appetite, vomiting, hematemesis, and melena are common.

The symptoms depend upon the degree of prolapse but are not sufficiently characteristic to permit a diagnostic conclusion without the characteristic roentgen finding: an "umbrella-like" or "mushroom-shaped" configuration in the base of the duodenal bulb. To be differentiated are pyloric carcinoma, pyloric ulcer, prolapsing gastric polyps, hypertrophic gastritis, duodenal ulcer, duodenal polyp, and hypertrophied pyloric sphincter.

Complications of prolapsed gastric mucosa are pyloric obstruction, ulceration and repeated hemorrhages. Surgical treatment is indicated for those cases in which a malignant neoplasm cannot be ruled out and those in which complications occur. Most cases will respond to treatment by bland diet and antispasmodics, sometimes combined with sedation.

Observations on 17 cases are presented in tabular form.

Five roentgenograms.

DONALD DEF. BAUER, M.D.
Coos Bay, Ore.

Unusual Aspects of Prolapsed Gastric Mucosa into the Duodenum. Francis W. Wilson and Leslie L. Lemak. *Am. J. Digest. Dis.* 19: 389-392, December, 1952.

Five cases are reported demonstrating some unusual aspects of prolapse of gastric mucosa into the duodenum.

In the first patient, there was a direct correlation between symptoms and roentgenological demonstration of the prolapse. It is also interesting to note that this patient was able to relieve his symptoms by right upper quadrant pressure.

In the second case the predominant symptom was severe retrosternal pain. The differential diagnosis lay between prolapse of the gastric mucosa and an atypical myocardial infarction. That the former condition was responsible for the pain is indicated by its relationship to food, absence of fever and of leukocytosis, a normal sedimentation rate, the prominent degree of prolapse demonstrated roentgenographically, and the relatively benign course.

The third patient presented a clinical and roentgenographic appearance typical of duodenal ulcer. The prolapse of the gastric mucosa into the duodenum first appeared during the healing of the ulcer. The fourth patient also first showed prolapse during the healing of a duodenal ulcer, and the authors suggest that this may be a transitory intermediate finding in the course of healing of a duodenal ulcer.

In the fifth patient, the prolapse of the mucosa was transitory, occurring only during episodes of active gastrointestinal hemorrhage. The authors feel that the prolapsed folds were the site of the hemorrhage on two separate occasions.

Five roentgenograms. DEAN W. GEHEBER, M.D.
Baton Rouge, La.

X-Ray Diagnosis of Inflammatory Changes of the Stomach. A. Mahlo. *Fortschr. a. d. Geb. d. Röntgenstrahlen* 77: 713-717, December 1952. (In German)

In general, gastroscopy has been considered superior

to roentgen studies in determining the presence of inflammatory conditions within the stomach, especially the demonstration of irregularity of the mucosal folds, rigidity, hypersecretion, and the occurrence of edema or infiltration. Even though certain parts of the stomach are not amenable to direct examination with the gastroscope, granular gastritis has been recognized by this means in between 30 and 40 per cent of cases with stomach symptoms. A radiologic diagnosis of this condition has seldom been made. The author believes that by the use of his technic it will be possible to demonstrate the finer changes in the gastric mucosa in a higher percentage of cases, and that a valuable addition will be made to our present diagnostic criteria.

A small amount of thin barium mixture is used to form a fine coating over the gastric mucosa, and very firm compression is applied. The shortest possible exposure with high-penetration technic and a minimal-focal-spot x-ray tube are recommended. Films are made on paper (Agfa). Extreme care is taken to avoid over-exposure or over-development. The patient is placed in the upright posture for examination of the fundus and turned in appropriate positions for other parts of the stomach, to make certain that too thick a barium layer does not remain in the area under examination. Films are viewed with a magnifier. The fine mucosal changes are not recognizable fluoroscopically.

The results of this technic, as described and illustrated, are remarkable for the fine detailed observation of gastric mucosa and the demonstration of minute changes. The author has shown the ability to recognize, by this means, about the same percentage of granular changes as are attributed to gastroscopy (30 per cent of cases giving positive results). Fine granular mucosal changes with elevation and coarse irregularity of the mucosal pattern, often true polypoid formations, were observed frequently in the fundus, pylorus, and to a lesser extent in the duodenum. Similar changes were seen in the efferent loop of jejunum in case of gastric resection. The mucosal pattern about gastric ulcer was demonstrated to much better advantage and the associated gastritis plainly recognized with this technic. A diagnosis of hypertrophic gastritis can therefore be established with considerable confidence. Atrophic gastritis cannot be definitely recognized, and the author depends on the lack of hydrochloric acid and gastroscopic observations for this diagnosis.

Eight roentgenograms. E. W. SPACKMAN, M.D.
Fort Worth, Texas

Suppurative Inflammation of the Gastric Wall. A Clinical, Anatomic and Radiologic Contribution. Mario Camplani. *Radiol. med. (Milan)* 38: 955-962, October 1952. (In Italian)

The author discusses the case of a patient who presented narrowing and irregularity of the pyloric canal with marked gastric retention. At surgery a resection of the pyloric antrum was done and the radiological appearance was found to be due to a subacute inflammatory process involving mainly the submucosa and muscularis, with the formation of small abscesses.

Three roentgenograms. CESARE GIANTURCO, M.D.
Urbana, Ill.

Epithelial Cyst of the Stomach. A Case Report. W. Ralph Deaton, Jr., and Elmer E. Pautler, Jr. *Ann. Surg.* 136: 898-900, November 1952.

The authors report a case of epithelial cyst of the

stomach, which is an extremely rare condition, only 48 cases having been previously recorded. The roentgen findings met all of Moore's qualifications for the roentgenographic diagnosis of a benign tumor of the stomach. The qualifications are:

1. They (benign tumors of the stomach) produce a filling defect that is circumscribed and punched out in appearance.

2. The defect is usually on the gastric wall, leaving the curvature regular and pliant.

3. While the rugae are obliterated in the immediate area of the tumor, just as in inflammatory and malignant lesions, those surrounding a benign tumor are more nearly normal in distribution and arrangement.

4. They cause little disturbance in peristalsis, and retention is uncommon except when the lesion is near or at the pylorus.

5. They do not reveal a niche, incisura, or other evidence of spasm.

6. They are rarely sufficiently large to be palpated.

Treatment consists of simple resection. It is important to make immediate diagnosis by frozen section technic to avoid unindicated massive resection of the stomach.

One roentgenogram; 1 photograph; 2 photomicrographs. DANIEL WILNER, M.D.

Atlantic City, N. J.

Peptic Ulcer: The Effect of Anticholinergic Drugs on the Mechanism of Pain. Walter L. Palmer, Firmin Vansteenhuyse, and Joseph B. Kirsner. *Am. J. M. Sc.* 224: 603-611, December 1952.

Twenty-six experiments were performed on 18 patients, 16 males and 2 females, ranging in age from twenty-three to sixty-two years. Eleven had duodenal ulcers, 5 gastric, 1 stomal, and 1 pyloric. Each had definite spontaneous pain of at least moderate severity. Ulcer sensitivity was proved by the appearance of pain following administration of hydrochloric acid through a Levin tube. With the onset of pain, the stomach was emptied and an anticholinergic drug was injected intramuscularly. Full effect of the drug was determined by the presence of side-effects. Hydrochloric acid was then again injected into the stomach, and the patient was asked to compare the persistent or recurrent pain with that present before the drug injection.

In 23 of the experiments the anticholinergic drug failed to prevent the induction of the pain. Only in 3 patients with duodenal ulcer did no pain occur. These results indicate that the relief obtained following the use of Banthine and other anticholinergic drugs is not due to desensitization of the pain mechanism, which still responded to the stimulus of hydrochloric acid in the customary manner. The relief is to be attributed rather to the fact that an inhibition or decrease in gastric peristalsis and tone slows the rate of gastric emptying and decreases the "acid attack" upon the ulcer. Some decrease in the secretion of acid further lowers the "acid attack." The result is a decrease of the inflammatory process, an elevation of the pain threshold, and a decreased exposure of nerve endings to acid stimulus. The lesion thus becomes insensitive to the normal stimulus of acid gastric juice and the "acid test," and also to the mechanical factors, such as peristalsis, which may evoke pain.

In 2 patients with sensitive gastric ulcers the behavior of the stomach was studied roentgenologically. The stomach was observed with and without pain, be-

fore and after administration of the anticholinergic drug. There was no direct relationship between pain and gastric or duodenal motility or spasm.

Four roentgenograms; 4 charts.

BERTRAM LEVIN, M.D.
Minneapolis, Minn.

Large Gastric Ulcers, Not Demonstrable at Roentgenologic Examination. Rudolf Schindler. *M. Clin. North America* 36: 1099-1110, July 1952.

Roentgen examination is the chief method for the diagnosis of gastric ulcer. However, roentgenologists know well that a certain percentage of gastric ulcers cannot be found even with very careful examination, including compression technic with spot films. The number of these apparently undiscoverable ulcers does not depend alone upon the skill and thoroughness of the observer. The number noticed depends greatly upon the number of checks either by gastroscopy or by exploratory laparotomy. In places where gastroscopy is done only in rare cases, as an exceptional procedure, the patient in whom nothing was found at x-ray examination will be discharged after treatment and nobody may discover that in fact he had a gastric ulcer. If gastroscopy is done in every instance in which gastric disease is suspected, but in which roentgenologic examination failed to reveal any pathologic change, then quite a few gastric ulcers are found. It must not be forgotten, however, that many gastric ulcers cannot be seen at gastroscopy, and thus some ulcers will be missed even when both methods are employed.

The author presents 5 cases showing that at times very large gastric ulcers, benign or malignant, cannot be demonstrated at x-ray examination, even by highly experienced and thorough examiners, who know in advance that the lesion is present. The various explanations given are not entirely satisfactory. Sometimes an ulcer crater may become so large that it looks like a simple continuation of the gastric cavity. Obviously, if the ulcer lies high on the lesser curvature, careful palpation is prevented by the overlying ribs. However, in only 2 of the author's cases was such a high-lying ulcer present. In the other cases the ulcer was located on the angulus or immediately beyond the angulus, so that the x-ray examination should have been easy.

All 4 cases of benign ulcer were characterized by a high-lying stomach which sometimes assumed the steer-horn form. In 1 case this high position was so marked that the shape of the stomach suggested an early volvulus. It is the belief of the author that we must become reconciled to the fact that x-ray examination of the high-lying stomachs and steer-horn stomachs is extraordinarily difficult and that in them even large localized lesions may be undiscoverable.

This explanation, however, does not cover the last case, that of a large carcinomatous ulcer. The stomach in this case was in normal position and of normal shape. It has been said that food or mucus may fill out the ulcer crater so completely that no barium can penetrate and no niche sign is produced. This may have been true in the case under discussion, because at gastroscopy the floor of the malignant ulcer was seen to be covered with thick mucus. This explanation, however, still does not account for the fact that the large stiff wall did not produce a marked filling defect, even on the spot films.

Five roentgenograms; 4 photographs; 2 photomicrographs; 2 tables.

BERT H. MALONE, M.D.
Brunswick, Ga.

Giant Benign Ulcerations of the Duodenum. J. F. Hamel. *Canad. M. A. J.* 67: 665-666, December 1952.

The majority of benign ulcers in the duodenal bulb are small, measuring from 0.1 to 1.0 cm. in diameter. In a review of the literature, however, the author found 12 cases with craters ranging from 2 cm. in diameter to 5×6 cm. He presents a case in which the dimensions were 5.0×5.5 cm. Of these 13 cases, only 5 were diagnosed antemortem.

In most of the cases reported the barium studies were considered normal because the ulcers were so large that they were interpreted as normal duodenal caps. Fluoroscopically, it was noted that the contrast material rushed into and filled the crater rapidly, but that the emptying time was slow and the walls of the crater remained smooth, rigid, and unchangeable. In the author's case the original examination was reported as showing a small ulcer. The patient died three months later and at autopsy the giant ulcer was found. The radiologist reviewing the films felt that the main reason for missing the greater part of the ulcer was its large size.

Since in all cases in which the diagnosis was missed death occurred as a result of hemorrhage, it is important that this entity be kept in mind, especially in cases with gastrointestinal symptoms and an apparently normal duodenal bulb on x-ray examination.

Two roentgenograms. JOHN M. KOHL, M.D.
Jefferson Hospital

Acute Perforation of a Duodenal Ulcer Immediately After Barium Meal, Complicated by Intestinal Obstruction. C. P. de Fonseca. *Lancet* 2: 1246-1247, Dec. 27, 1952.

Though exact figures of incidence are not available, perforation of a peptic ulcer during or immediately following a barium meal is certainly a rare occurrence. In the case reported here the perforation was in the duodenum at the site of an ulcer demonstrated on the films for which the barium was administered. Symptoms ensued almost immediately after the administration of the barium meal and operation was performed the next day. The entire peritoneum and all the visceral surfaces were smeared with barium intimately mixed with exudate. As much of this as possible was removed and the perforation was closed. Convalescence was complicated by intestinal obstruction due to retained barium. Relief ensued after a large amount of barium and flatus was passed following a colonic irrigation.

Two roentgenograms.

The Afferent-Loop Syndrome. Biliary Regurgitation After Subtotal Gastrectomy and Its Relief. Charles A. Wells and I. W. MacPhee. *Lancet* 2: 1189-1193, Dec. 20, 1952.

The so-called afferent-loop syndrome following subtotal gastrectomy, and characterized by bilious regurgitation, is a result of kinking in the afferent loop of the gastrojejunal anastomosis at its junction with the stomach. Within an hour or less after a meal the patient may complain of a bitter taste in the mouth and the regurgitation of yellow, green, or brown bile, quite unmixing with food. Often, however, there may be a retention of pancreatic and biliary secretions, causing epigastric pain and discomfort relieved suddenly by bilious vomiting without relation to meals.

Roentgenographically, the remnant of stomach ap-

pears normal, and barium may be seen to pass rapidly and freely down the efferent limb of the anastomosis but *does not enter the afferent loop*.

Goligher and Riley (Lancet 1: 630-636, 1952. Abst. in Radiology 61: 451, 1953) are cited by the authors as stating that the type of anastomosis has little bearing on the occurrence of postprandial symptoms following gastrectomy. As regards rapid emptying, efferent-limb symptoms, and malnutrition, they are in agreement with this view. Afferent-loop stasis, on the other hand, is seen especially following the Finsterer-Lake type of antecolic right-to-left anastomosis associated with a Hofmeister valve. It is sometimes observed in the retrocolic Polya type of anastomosis. It rarely follows gastroenterostomy and the older limited partial gastrectomy with Polya anastomosis.

In a series of 293 gastrectomies for peptic ulcer, the authors found an incidence of bilious regurgitation of six months duration or longer in 53. Of 31 patients in whom the condition was described as severe, 16 had been subjected to operation, with relief of symptoms in all. Operative measures are discussed, and illustrative case histories are presented. A brief consideration of afferent-loop reflux concludes the paper.

Six roentgenograms; 2 diagrammatic drawings.

A Teaspoonful of Baking-Soda. A. J. Glazebrook and Fred Wrigley. Lancet 2: 1097-1100, Dec. 6, 1952.

Since sodium bicarbonate, or ordinary baking soda, is a major constituent of both bile and pancreatic secretions, it seemed to the authors that adequate amounts of it are probably essential for proper functioning of the small bowel. This they felt would explain the therapeutic efficacy claimed by many patients for baking soda in the relief of postgastrectomy symptoms.

To test this idea, 18 patients with the postgastrectomy syndrome were examined by means of a barium-dextrose mixture and again after administration of the same mixture with the addition of 4 gm. of sodium bicarbonate. In 14 of the group the sodium bicarbonate quieted the peristaltic rushes and spasms produced by the sugar in the barium meal. Some patients were subsequently given atropine or a synthetic spasmolytic agent, Ro 2-3773, and a similar effect was observed.

Ten roentgenograms.

Roentgen Appearance of the Small Intestine in Tuberculous Peritonitis Before and After Streptomycin Therapy. John T. Brackin, Jr., Joseph M. Miller, and William H. Bell. Am. J. Roentgenol. 68: 887-893, December 1952.

Since the advent of the treatment of tuberculosis with Streptomycin, several clinical reports on its use in tuberculous peritonitis have appeared. To the authors' knowledge, theirs is the first report on roentgen studies of the small intestine in patients with tuberculous peritonitis thus treated.

They present three cases, proved by exploration and biopsy, showing an abnormal small bowel pattern. Delayed motility, segmentation, loss of outline of the valvulae conniventes, and dilated segments were the principal pre-treatment findings. Following Streptomycin therapy the small bowel pattern returned to normal, though one patient required a second course of the drug.

The mechanism of the production of the altered appearance of the small bowel in tuberculous peritonitis is unknown. Adhesions, damage to the intramural nerve

fibers, and lymphatic obstruction are factors which may singly or in combination produce the changes. Secondary deficiency disease may also contribute to the observed changes.

Eighteen roentgenograms.

M. HARLAN JOHNSTON, M.D.
Jacksonville, Fla.

Pneumatosis Cystoides Intestinalis. Benjamin Sherwin and Abba A. Messe. Ann. Surg. 136: 893-897, November 1952.

The authors present a case of pneumatosis cystoides intestinalis, a rare condition, since only 43 cases could be found in the American literature. The condition is referred to, also, as gas cysts of the intestine. The exact pathogenesis has not been established, although the most logical explanation is on a mechanical basis. According to one such theory, the gas is forced from the bowel lumen through a mucosal defect in the intestinal wall. A more recent view (Stiennon: Am. J. Dis. Child. 81: 651, 1951. Abst. in Radiology 58: 607, 1952) holds that the gas reaches its diverse situations by retroperitoneal extension from a peptic ulcer. Once having reached the mesenteric insertion on the intestine, the gas may extend into the subserosal spaces or may follow the perforating blood vessels and enter the submucosal space.

The roentgen examination in the present case revealed a markedly dilated stomach with almost complete pyloric obstruction. A gallbladder series was negative except for marked gaseous distention of the bowel in the liver region, and a barium enema study showed the same rather bizarre distribution of gas, which the radiologist stated might or might not be due to organic disease.

At operation, several loops of small bowel between the right lobe of the liver and the dome of the diaphragm were found coiled and matted together by fibrous adhesions. There were innumerable gas-containing cyst-like structures in the serosa of the bowel. These cysts varied in size from a few millimeters to about 5 cm. in diameter, and some of them contained old blood as well as gas. The involved segment of bowel was resected and an end-to-end anastomosis performed.

Two roentgenograms. DANIEL WILNER, M.D.
Atlantic City, N. J.

Intestinal Pneumatosis. R. R. Anderson and E. F. Geever. Am. J. Digest. Dis. 19: 385-389, December 1952.

A case of intestinal pneumatosis in an elderly white male is reported. A 144-cm. segment of jejunum was removed surgically during the course of the treatment. Diverticula were present in this portion of small bowel, but did not appear to be related to the disease. The authors feel that there was unquestionable increased permeability of the mucous membrane, which allowed gas to enter and dilate the lymphatic channels. Hypertrophy of the longitudinal and circular muscle layers was noted microscopically.

Although in other cases reported the process has been considered to be initiated by a partial obstruction and a break in the mucosa, there was no evidence of obstruction in this patient, nor was there any evidence to support the theory that excessive air swallowing was an etiologic factor.

The authors feel that the term "intestinal pneuma-

tois" should be restricted to those cases where the process extends through the wall into the mesentery, and in which gas is also demonstrable in the subdiaphragmatic regions on roentgenographic studies. They believe that there may be simple diffusion of air into the free peritoneal cavity as well as dissection along the root of the mesentery to the retroperitoneal space.

Three roentgenograms: 1 photograph; 2 photomicrographs.

DEAN W. GEHEBER, M.D.
Baton Rouge, La.

Radiologic Demonstration of Ileal Obstruction Due to Invaginated Meckel's Diverticulum. Antonio Lurà. *Rev. ital. di radiol. clin.* 2: 182-190, October 1952. (In Italian)

The author describes a case of invagination of a Meckel's diverticulum with low ileal obstruction. This invagination was apparently caused by a lipoma attached to the end of the diverticulum. The condition was demonstrated by ileal reflux from a barium enema as well as by a "small intestinal enema." The radiographs show a typical image of invagination about 15 cm. proximal to the ileocecal valve. The author states that this case is the second one observed radiologically (a similar case was reported by Laurell: *Acta radiol.* 13: 362, 1932). In 1925, Lower (*Ann. Surg.* 82: 436, 1925) was able to find 54 such cases reported by surgeons and pathologists.

Five roentgenograms; 2 photographs; 1 drawing.
CESARE GIANTURCO, M.D.
Urbana, Ill.

Diagnosis and Treatment of Adenomatous Polyps of Colon. Russell R. Klein and Robert A. Scarborough. *Arch. Surg.* 65: 65-70, July 1952.

The passage of gross blood per rectum from a source above reach of a proctoscope is most commonly from a colonic neoplasm, either benign or malignant. Ninety-five per cent of benign lesions are precancerous adenomatous polyps, whose discovery and eradication may prevent the development of carcinoma. Diagnosis of such lesions is dependent upon the judicious use of competent roentgenologic technic and barium-air contrast enema examination.

The four specific indications for roentgen examination of the colon in the investigation of bleeding per rectum are (1) failure to demonstrate the source of bleeding by adequate anoscopic and proctoscopic examination, (2) evidence of blood in the lumen of the upper rectum on proctoscopic examination, (3) presence of a sentinel polyp, and (4) description by the patient of bleeding that suggests a higher source.

The accuracy of diagnosis of polyps of the colon rests with the roentgenologist. It is the responsibility of the surgeon to select the proper subjects for x-ray examination, to insist upon an adequate examination, and to request repeated examinations when the clinical evidence is indicative of the presence of an unidentified lesion. Not infrequently a second or third examination is required before a polyp is demonstrated. In one instance of persistent colonic bleeding, after three x-ray examinations and an exploratory laparotomy failed to reveal the source of the hemorrhage, four more x-ray examinations were done before a small benign polyp was located and subsequently removed at a second laparotomy.

Certain features of the x-ray examination should be emphasized:

1. Adequate preliminary preparation of the colon is imperative to avoid false shadows simulating polyps. At least 2 oz. of castor oil taken eighteen hours before examination, with subsequent restriction to a liquid diet without milk, is preferred.

2. An adequate number of spot-films should be taken at suitable angles to unfold and visualize all overlapping loops of the bowel. Multiple films of the sigmoid colon should be made from various angles, since this is the most frequent site for colonic polyps.

3. There should be effective utilization of the air-contrast technic, employing horizontal-ray examination with the patient in the right prone, left prone, and upright positions.

4. The presence of diverticula, particularly the presence of distortions resulting from diverticulitis, often masks the coexisting polyp. Frequently, the presence of gross blood in the stool is attributed to diverticulosis or diverticulitis. Some authorities state that bleeding is commoner from this source than from carcinoma. In the authors' experience, however, such bleeding has usually been found to be due to a coexisting neoplasm, often a single adenomatous polyp.

5. The presence of a polyp should be adequately demonstrated on the x-ray films before such diagnosis is accepted as indication for laparotomy. Unless a definite pedicle is visualized, confirmation of the apparent lesion by a second examination is advisable.

In 100 patients with adenomatous polyps of the colon, 81 per cent of the polyps were in the sigmoid. In 85 per cent there was present a single polyp. In 14 per cent two polyps were found, and in 1 per cent there were three polyps. In three out of four patients, the lesions were benign, and simple polypectomy was performed. In 11 per cent malignancy was proved by frozen-section examination, and radical segmental resection was done. In 5 of these 11 patients regional lymph node metastases had already occurred. In 12 per cent small foci of carcinoma were found by permanent-section examination only, in otherwise benign adenomas. Radical resection was not carried out in these 12 patients.

Three illustrations. BERT H. MALONE, M.D.
Brunswick, Ga.

Roentgen Demonstration and Significance of the Pedicle in Polypoid Tumors of the Alimentary Tract. Barton R. Young and Robert L. Scanlan. *Am. J. Roentgenol.* 68: 894-898, December 1952.

The roentgen demonstration of a pedicle associated with a filling defect is pathognomonic of a polypoid tumor. The pedicle is produced by traction as the tumor is stripped away from the muscular coat by peristaltic action. Tumors with long pedicles have narrow bases and those with short pedicles have broad bases. The permanency of the pedicle is related to the loss of elasticity as a result of prolonged traction.

Indentation of the intestinal wall may be the first evidence of a pedunculated tumor and makes necessary a careful search for a pedicle. The authors rely mainly upon roentgenoscopy and spot films for demonstration of the tumor and its pedicle. They use double-contrast studies for orientation and to exclude other lesions.

The precise localization of pedunculated tumors is important because it may be impossible to palpate them through the bowel wall at surgery.

Twelve roentgenograms; 1 photograph.

M. HARLAN JOHNSTON, M.D.
Jacksonville, Fla.

Perforation of Apparently Normal Colon After a Barium Meal. J. C. B. Serjeant and J. A. Raymond. *Lancet* 2: 1245-1246, Dec. 27, 1952.

Several instances of perforation of a diseased colon after a barium meal or enema have been previously reported. The authors' case is unique in that perforation occurred in an apparently normal colon. Barium was administered orally following a provisional diagnosis of nervous dyspepsia. On the next day, symptoms of peritonitis developed, and roentgen examination showed, in addition to discrete masses of barium in the colon, a dense collection in the pouch of Douglas, with thinner streaks in the left paracolic gutter and between loops of bowel. At laparotomy a perforation was discovered in the pelvic colon about 2 inches above the peritoneal reflection. The colon was otherwise normal throughout.

Recovery followed closure of the perforation and proximal colostomy. Barium masses removed at operation were difficult to cut with a scalpel but disintegrated in water.

Three roentgenograms.

Intraperitoneal Escape of Barium Enema Fluid. Perforation of Sigmoid Colon. Ivan Isaacs. *J.A.M.A.* 150: 645-646, Oct. 18, 1952.

Two patients with perforation of the sigmoid colon are reported in this paper. The radiologic findings in the two cases were strikingly similar and included a particular sign that may be of value for the prompt recognition of such a perforation during roentgenoscopy. The barium escaping through a perforation in the sigmoid immediately collected in the space between the descending and sigmoid colon and the left lateral abdominal wall. The density of this free barium enables it to be visualized alongside the opacified colon, with the fluid showing a smooth left border where it is delimited by the parietal peritoneum. This may appear as a linear streak of density external to the bowel and distinctly separated from but parallel to the descending or sigmoid colon. Such an appearance was noted on the radiographs of both patients in this report.

If the radiologist is alert to the possibility and can promptly recognize the appearance of the free escape of barium fluid from the colon, it may be possible to limit the degree of insult by immediate termination of the enema and prompt laparotomy.

Three roentgenograms. DANIEL WILNER, M.D.
Atlantic City, N. J.

Clinical Studies on Effect of Barium in the Peritoneal Cavity Following Rupture of the Colon. Norman Zheutlin, Elliott C. Lasser, and Leo G. Rigler. *Surgery* 32: 967-979, December 1952.

This paper is a study of the answers to a questionnaire sent to approximately 100 teaching institutions throughout the country. Fifty institutions reported that they had never had a case of rupture of the colon in the course of a barium enema. Thirty-four stated that they had at some time encountered this accident. Several of these reported more than one case, bringing the total number to 50. These, plus 3 reported by the authors, furnish 53 cases for analysis.

Perforations of the colon occurred most commonly in three types of examination. Thirteen cases appeared in the examination for suspected carcinoma, 12 in re-evaluation of the colon through a colostomy opening, and 8 in suspected colonic obstruction. The large num-

ber of cases occurring in examinations performed through a colostomy opening was surprising.

In 35 of the 49 cases where the information was available, the rupture in the colon occurred during the course of the barium enema. In 7 cases the colon was thought to have ruptured immediately following the enema, in 1 case twenty-four hours later. In 4 rupture was present when the enema was administered.

The overall mortality rate among those treated surgically was 47 per cent as opposed to an overall mortality rate of 58 per cent in the group treated by conservative measures. Among those in the surgical group, approximately 53 per cent were listed as being in good or fair condition immediately following the rupture, while approximately 47 per cent were listed as in poor condition or moribund. These figures were almost identically reversed in the group treated conservatively. This may have been a factor in the slight difference in overall mortality rates between the medical and surgical groups. The operative survival appears to be greater if surgery can be carried out within three hours of the perforation. Clinically significant adhesions developed in 30 per cent of 23 cases followed for an average of eighteen months. Adhesions were as frequent in those cases where an attempt was made to remove the barium sulfate as in those cases treated conservatively.

The authors supplemented their observations by an experimental study on guinea-pigs receiving intraperitoneal injections of barium sulfate.

Eleven roentgenograms; 4 photomicrographs; 2 tables. HOWARD L. STEINBACH, M.D.

University of California

Unusual Roentgenographic Findings in Gangrenous Appendicitis. J. E. Musgrove. *Canad. M. A. J.* 67: 666-667, December 1952.

The author reports a case of gangrenous appendicitis in a 30-year-old white farmer. The physical findings were such as to suggest a diagnosis of appendicitis with peritonitis or ruptured peptic ulcer with leakage down the right colic gutter.

Roentgenograms taken in the erect and supine positions showed absence of free air under the diaphragm and moderate distention of the colon and a few loops of small intestine. The appendix itself appeared to be outlined by air in its lumen. It was quite high in the right lumbar gutter and was retrocecal. This unusual finding was thought to be due to complete obstruction at the base of the appendix causing a mechanical appendiceal ileus.

At operation the appendix was found to lie high in the retrocecal position and to be gangrenous from base to tip. The base was completely obstructed. No reference to a similar roentgenographic report could be found in the literature.

One roentgenogram. JOHN M. KOHL, M.D.
Jefferson Hospital

Hernia Through the Foramen of Winslow. J. L. Smoot. *Ann. Surg.* 136: 1040-1043, December 1952.

This is a clinical report of a case of hernia through Winslow's foramen previously reported by Cimmino in *RADIOLOGY* (60: 57, 1953).

"Laparoscopic" Cholangiography (Direct Cholangiography). M. Royer. *Fortschr. a. d. Geb. d. Röntgenstrahlen* 77: 690-705, December 1952. (In German)

The author discusses the use of cholangiography pre-

operatively, during operation, and postoperatively, as well as in non-surgical cases. The method which he describes involves the use of the laparoscope (Ruddock), which is inserted 6 to 10 cm. to the right of the mid-line. For the cholangiographic procedure a special cannula 1.5 mm. in diameter and 7 cm. in length is inserted three to four finger breadths to the right of the mid-line just below the liver edge. A special needle 1 mm. in diameter and 17 cm. in length is inserted through this cannula and punctures the gallbladder. The distal end of the needle tapers out to a fine point, 0.5 mm. in diameter and 15 mm. in length, to facilitate insertion. A steel sound, 0.8 mm. in diameter and 20 cm. in length, is also inserted through a cannula 1.2 mm. in diameter and used to displace organs and tissues which interfere with visualization of the gallbladder. Twenty to 50 c.c. of contrast medium are injected directly into the gallbladder by this means (Nosylan, Abrodil, Hippuran, Nytasom, or Diodrast). After inserting the special needle, 2 to 3 c.c. of bile is withdrawn for microscopic and bacteriologic study, and the medium is introduced.

By this method, the gallbladder appears slightly larger than with the usual procedure; Heister's valve is seen in most cases; the intrahepatic ducts are not filled, but the cystic and common ducts are well visualized and entrance of the contrast material into the duodenum is demonstrable.

Peristalsis of the gallbladder has not been observed by the author, but the organ contracts symmetrically, and transverse indentations have been observed similar to the haustra of the colon. Emptying as observed by this method is somewhat slower than in the usual study. No peristaltic activity has been demonstrated in the ducts, contrary to reports of other investigators. The author states that there is not necessarily a widening of the ducts postoperatively. He observed one patient eight years after operation with no duct widening. In 5 cases with a completely non-functioning organ the ducts were not widened and in 3 cases obstruction by stone was not accompanied by abnormally wide ducts.

One of the chief advantages in this type of study is the preoperative identification of stones in the cystic and common ducts. In these cases, dilatation of the proximal portion of the duct is visualized. The position and number of stones are of great importance to the surgeon.

The author briefly summarizes case reports in which this method has demonstrated its advantage: (a) stones present in gallbladder and cystic duct with no colic or icterus; (b) lithiasis of the gallbladder and duct, with cholecystitis; (c) hepatic colic resulting from stones in the ducts, with no icterus; (d) calculi and jaundice without pain; (e) cholecystitis associated with duodenal ulcer; (f) biliary tract dyskinesia; (g) tumors (both benign and malignant).

There have been no untoward results with the method. A few patients have shown peritoneal irritation, which disappeared in a few days with bed rest and ice packs to the abdomen. It is not always possible, however, to obtain satisfactory injection. Failure may be due to (1) unsatisfactory position of the laparoscope, (2) atony of the gallbladder, making puncture difficult or impossible, (3) a position of the gallbladder making visualization impossible, (4) plugging of needles by inspissated bile, blood clot, etc., (5) adhesions, (6) an empty organ at the time of examination, (7) an organ which is shrunken from disease, (8) the presence of a large calculus.

The method is as yet in a stage of trial and far from technical completion.

Twenty roentgenograms; 2 drawings.

E. W. SPACKMAN, M.D.
Fort Worth, Texas

A Method to Improve Roentgen Diagnosis of Biliary Diseases with Bile Acids. Alfred M. Berg and Joseph E. Hamilton. *Surgery* 32: 948-952, December 1952.

Ten patients who received a double dose of Priodax, without visualization of the gallbladder, were treated with bile acids (Decholin or Ketochol) for five to thirty-two days, after which cholecystography was repeated. In 7 patients concentration of the radiopaque material was then sufficient for roentgen diagnosis. Two of the cases were eventually diagnosed as pancreatitis, and 1 as hepatitis. In 2 patients, radiolucent stones became visible. In 2 others the gallbladder was poorly visualized and it was felt that they probably had a mild cholecystitis with impaired function. In the 3 cases with continued failure of visualization following the course of bile acids, severe disease of the gallbladder was subsequently found at surgery.

It is thought that the bile acids relieve the biliary stasis which is frequently the cause of non-visualization of the gallbladder.

Two roentgenograms; 1 table.

HOWARD L. STEINBACH, M.D.
University of California

Carcinoma of the Tail of the Pancreas Associated with Bleeding Gastric Varices and Hypersplenism. Leon J. Marks, Berthold Weingarten, and George R. Gerst. *Ann. Int. Med.* 37: 1077-1084, November 1952.

The authors report an unusual case of carcinoma of the tail of the pancreas manifested by massive melena, gastric varices, and a peripheral blood picture of hypersplenism. Initial radiographic examination of the upper gastrointestinal tract revealed no evidence of esophageal varices. A diagnosis of fundal varices was considered, but fundal carcinoma could not be ruled out. In addition the splenic shadow was enlarged.

Subsequent surgery revealed numerous large varicosities in the fundus. The spleen was enlarged to about three times its normal size. There was an intrinsic mass in the tail of the pancreas which apparently obstructed the venous pathways from the spleen. A splenectomy and hemipancreatectomy were performed.

The patient died seven months later, and autopsy revealed adenocarcinoma of the body of the pancreas with metastasis to the liver, abdominal lymph nodes, mesentery, stomach, duodenum, and transverse colon. There were thrombi in the pulmonary arteries, as well as multiple pulmonary infarcts.

Radiographically gastric varices are difficult to differentiate from gastric neoplasm, especially in the absence of esophageal varices. The presence of splenomegaly, as in this case, is more suggestive of gastric varices than of carcinoma. Splenectomy in this instance resulted in the correction of the blood picture and the disappearance of the varices with cessation of the gastrointestinal bleeding. Carcinoma of the tail of the pancreas as a cause for the syndrome of hypersplenism with cytopenia must be rare, judging from the lack of reports in the literature.

Two roentgenograms. ROBERT H. LEAMING, M.D.
Memorial Center, N. Y.

THE MUSCULOSKELETAL SYSTEM

Centers of Ossification of the Skeleton. Bertram R. Girdany and Ross Golden. *Am. J. Roentgenol.* 68: 922-924, December 1952.

In 1931, Camp and Cilley published a chart with diagrams of the ossification centers in the human skeleton showing average time of appearance and fusion (*Am. J. Roentgenol.* 26: 905, 1931). The authors have revised this chart in the light of additional information gained in the last twenty years.

Two charts. M. HARLAN JOHNSTON, M.D.
Jacksonville, Fla.

The Roentgen Diagnosis of Neoplasms of Bone. Ralph S. Bromer. *S. Clin. North America* 32: 1745-1759, December 1952.

In no other field of roentgen diagnosis does the roentgenologist have greater responsibility than in the differentiation of benign and malignant bone lesions. The "film diagnosis" of bone tumors is not only antiquated; it is dangerous. The roentgenologist should be aware of the complete clinical picture and objectively study the film before attempting a diagnosis. In his report, he should mention the pathologic changes which might produce these findings and be consistent with the clinical picture.

It is impossible for the roentgenologist to determine the histology of neoplasms, and frequently he cannot determine the type of benign or malignant process. The importance of biopsy, therefore, cannot be over-emphasized. According to Lichtenstein, no bone tumor should be treated before histologic verification. The "therapeutic test" by roentgen treatment prior to biopsy is to be condemned.

The roentgenologist can be of assistance in selection of the site for biopsy. He must assist, also, in the decision as to whether the evidence obtained roentgenologically warrants immediate biopsy or surgical exploration. Should the lesion appear inflammatory, the decision must be made as to whether antibiotics should be used and progression or regression of the lesion be awaited.

The first requisite in the differentiation of benign and malignant lesions is determination of invasion into surrounding normal bone or soft tissue. The former is quite difficult, as the bone changes may be represented by either increased or decreased bone density. Soft-tissue invasion is manifested by perpendicular striations at right angles to the shaft. This change is not always characteristic and is not diagnostic. Certain cases of periosteal fibrosarcoma of bone reveal an expanding soft-tissue mass with practically normal appearing underlying bone. Subperiosteal extension with cortical perforation is a sign of malignancy, and is found in approximately half of the cases of osteogenic sarcoma. If necessary, two sets of exposures should be made to demonstrate bone structure and soft tissues, respectively.

Significant characteristics of each of the malignant neoplasms involving bone are briefly summarized. Benign lesions other than osteomyelitis which cause diagnostic difficulties are osteoid osteoma, sclerosing osteomyelitis of Garré, cystic changes in hyperparathyroidism, eosinophilic granuloma, fatigue fractures, periosteal injuries, and ossifying hematomas.

Four roentgenograms; 2 photomicrographs.

M. HARLAN JOHNSTON, M.D.
Jacksonville, Fla.

Paget's Disease (Osteitis Deformans). Review of One Hundred Eleven Cases. J. A. Rosenkrantz, Julius Wolf, and John J. Kaicher. *Arch. Int. Med.* 90: 610-633, November 1952.

This study is based on a review of the clinical records of 111 patients with Paget's disease of bone. The causative factor of the disease is not known. Chronic inflammation, syphilis, toxic irritation with disturbed metabolism and disturbed endocrine function affecting bone metabolism have been indicted. The average age of the 111 patients was fifty-five years. The average age at onset was forty-one years. Approximately 14 per cent of the patients were aware of their disease between the ages of twenty-one and thirty. Race was not a significant factor. Approximately 10 per cent of the patients were Negro; the remainder were white. This corresponded to the ratio of Negro to white patients admitted to the hospital from which the report comes.

Patients with osteitis deformans frequently have no symptoms referable to this disorder, and its discovery may be incidental to other roentgenologic studies. Fifty-five patients complained of bone pain. Other symptoms were defective hearing, visual disturbances, tinnitus, fatigue, headaches, urinary complaints and calculi, dyspnea, increasing head size, gait disturbances, vertigo, angina pectoris, swelling and ulceration over affected bone parts, and reduction of stature in the later stages.

The physical findings most frequently noted were neuromuscular disturbances, 45 patients having sensory, reflex, motor, gait, and central nervous system changes. Other findings were cardiac abnormalities, obesity, prominence of the skull or jaw, bowing of the lower extremities, emphysema or increased anteroposterior chest diameter, hypertension, increased height, deformity of the pelvis or hip, and deformity of the clavicle.

Biochemical analyses revealed normal serum calcium and inorganic phosphates. The serum alkaline phosphatase was elevated in most instances, while serum acid phosphatase was usually normal except in rare cases with markedly elevated alkaline phosphatase, in which it too was elevated.

Roentgenologic studies revealed the pelvic bones to be involved most frequently, followed by the skull, femur, lumbar spine, thoracic spine, tibia, humerus, cervical spine, scapula, clavicle, sacrum, ribs, fibula, and mandible. Seventeen patients had roentgen evidence of pathologic fracture through the involved bone.

Four roentgenograms; 3 photomicrographs; 2 charts; 10 tables.

HOWARD L. STEINBACH, M.D.
University of California

Polyostotic Fibrous Dysplasia—A Case Presentation. E. R. Harrigan. *J. Canad. A. Radiologists* 3: 69-73, December 1952.

Fibrous dysplasia may involve one or many bones. When widespread, it tends to be predominantly unilateral. The roentgen picture shows in some areas a coarse, fibrous, irregular strand-like pattern due to the poorly organized trabecular calcification in the fibrous tissue. Elsewhere there may be a hazy, ground-glass appearance, the result of fibrous tissue replacing bone, and not as a result of true cystic change. Some of the radiolucent areas are fairly well outlined by a thin, dense line of demarcation. Others merge with the adjacent bone. The type of bony change is extremely

varied. It may be discrete or involve a whole bone. The marrow cavity of the involved bone may be widened, the bone expanded, and the cortex thinned. Early appearance and fusion of secondary ossification centers is a common feature in females. Elongation or bowing of bones may be present. Cranial nerve palsies may occur as a result of narrowing or deformity of the various cranial foramina.

A characteristic feature of the disease is the normal structure of the uninvolved area. This, in addition to the predominantly unilateral distribution of the lesions, aids in distinguishing the condition from osteitis fibrosa cystica generalisata due to hyperparathyroidism. Normal calcium and phosphorus values corroborate the radiographic distinctions from hyperparathyroidism. Associated congenital anomalies are common.

The author presents the case of a 9-year-old girl who showed precocious sexual development. She had begun to menstruate at the age of two and had had an intermittent vaginal discharge since the age of three months. There was advanced bone maturation, the bone age being about fourteen. Roentgenograms showed a coarse, irregular, mottled and strand-like increase in density involving the left fifth metacarpal and phalanges and the left fourth and fifth metatarsals and phalanges. The left tibia and fibula and femur showed changes varying from a radiolucent to a ground-glass density. There were thickening and increase in the density of the occipital bone. The patient had suffered fractures of the left fourth and fifth metatarsals as a result of minor trauma. Previous laparotomy showed no abnormalities of the ovaries. An associated finding was bilateral double kidney pelvis and ureters.

Seven roentgenograms; 2 photographs.

MORTIMER R. CAMIEL, M.D.
Brooklyn, N. Y.

Chondroectodermal Dysplasia (Ellis-Van Creveld Disease). Report of Three Cases. John Caffey. *Am. J. Roentgenol.* 68: 875-886, December 1952.

The Ellis-Van Creveld syndrome, first described in 1940 (Ellis and Van Creveld: *Arch. Dis. Childhood* 15: 65, 1940) is a distinct entity with definite distinguishing characteristics which allow it to be differentiated from other types of dysplasia and dwarfism. Caffey here presents 2 new cases and reports further on a 19-year-old patient previously reported (see reference above).

In these 3 cases and the 2 others previously recorded by Ellis and Van Creveld the changes have been severe and consistent. The constant lesions are hypoplasia of the teeth and nails; progressive shortening distalward of the bones in the arms and legs, with the most severe changes in the terminal phalanges, bilateral manual polydactylism and polymetacarpalism; synmetacarpalism; and bilateral fusion of the capitate and hamate bones. The tibiae in every instance presented a widened proximal end with long lateral and short medial slopes, the latter being capped by thin hypoplastic ossification centers in the proximal tibial epiphyseal cartilage.

Inconstant findings are alopecia, fusion of the upper lip and gum, congenital malformation of the heart, dislocation of the radial heads, polydactylism and syndactylism in the feet and polymetatarsalism.

This syndrome is easily differentiated from achondroplasia by the progressive distal shortening of the bones of the extremities. The fibula is relatively the shortest

bone in the leg in chondroectodermal dysplasia while it is relatively the longest in achondroplasia.

Fifteen roentgenograms; 16 photographs.

M. HARLAN JOHNSTON, M.D.
Jacksonville, Fla.

Primary Hyperparathyroidism Requiring Prolonged Postoperative Therapy. Irwin S. Eskwith. *Ann. Int. Med.* 37: 1247-1253, December 1952.

A case of parathyroid adenoma of long duration is reported. The diagnosis was made and operation was performed at the age of sixty-two, though renal calculi, frequently the first sign of the disease, had been removed thirty-two years previously. An outstanding feature of the case was the intensive postoperative therapy required to restore calcification of the bones and maintain the serum calcium at a satisfactory level.

Marked decalcification of the skeletal system was demonstrated prior to operation. Following removal of the adenoma, large amounts of calcium were administered over a long period, the "hungry bones" consuming it "as a man lost in a desert consumes water when it is offered to him."

In his conclusions the author states that his case "illustrates that osteitis fibrosa cystica, when the cause is removed, may result in such rapid and prolonged withdrawal of calcium from the serum that an adequate serum level of this substance is almost impossible to maintain. Thus tetany and paresthesias identical with those of true hypoparathyroidism may occur. Before concluding that this latter syndrome exists, films of the bones should be obtained. If these continue to show marked decalcification, the probable cause of the tetany is bone hunger, and intensive therapy of the type herein described should be carried out until recalcification seems adequate." The prolonged treatment with large amounts of oral and intravenous calcium was of no harm in the case reported, and roentgenograms obtained two years after operation are reproduced, showing recalcification of the skull, clavicles, and ribs.

Four roentgenograms; 1 graph.

STEPHEN N. TAGER, M.D.
Evansville, Ind.

Vitamin D Intoxication. A Report of Four Cases. S. G. Ross. *J. Pediat.* 41: 815-822, December 1952.

The presence of vitamin D intoxication should be suspected when a history of prolonged administration of high doses of vitamin D is accompanied by anorexia, loss of weight, diarrhea, loss of activity, and extreme weakness. The calcium and frequently the phosphorus concentration in the blood are increased. At first there are excessive deposition of calcium salts at the provisional zone of calcification and increased mineralization of the bone trabeculae. If the hypervitaminosis is prolonged and of sufficient severity, heightened excretion of calcium by the kidney follows, and the calcium and phosphorus retention in the body is decreased. At the same time, metastatic calcification of different organs of the body develops, particularly the media of the blood vessels, the kidneys, the heart, the stomach, the lungs, and the adrenals.

Four cases of vitamin D intoxication in infants are presented. The roentgenograms demonstrated the demineralization of the skeleton and increased density in the provisional zone of calcification and, proximal to

this, a broad area of rarefaction indicating decalcification. Some subperiosteal calcification was demonstrated surrounding the long bones.

Three roentgenograms; 6 photomicrographs.

HOWARD L. STEINBACH, M.D.
University of California

Deformity of Vertebral Bodies in Cretinism. Philip Rainsford Evans. *J. Pediat.* 41: 706-712, December 1952.

Anomalies of the lower thoracic and upper lumbar vertebral bodies similar to those found in gargoylism may be seen in cretins. Of 13 cretins examined, 1 had a normal spine, 5 had minor abnormalities, and 7 showed deformity of the bodies of the twelfth thoracic or first or second lumbar vertebra. Kyphosis with subsequent bony abnormality developed between the ages of six months and two and a half years.

A similar abnormality of the vertebral bodies has been described in achondroplasia and gargoylism. The pathological changes in these three conditions are not identical, but in all there is deficient bone formation at the epiphyseal line, as well as disorderly arrangement of cartilage columns, with degeneration of cartilage. Proliferation of cartilage is irregular and often deficient, and is probably the essential abnormality which permits the formation of these dysplastic vertebrae. The affected vertebrae are those most subject to trauma, and the abnormality is probably caused by the stress of flexion acting on chondrodystrophic vertebral bodies.

The deformity may disappear under treatment with thyroid extract.

Eight roentgenograms; 1 photograph.

HOWARD L. STEINBACH, M.D.
University of California

An Analysis of One Hundred Consecutive Lumbar Myelograms Followed by Disc Operations for Relief of Low-Back Pain and Sciatica. Lee T. Ford, Robert H. Ramsey, Earl P. Holt, and J. Albert Key. *Surgery* 32: 961-966, December 1952.

An analysis was made of 100 consecutive cases in which a hospital work-up, including myelograms, had been carried out prior to intervertebral disk operation. Pathologic disks were found at operation in 96 patients and normal disks in 4 patients.

Twelve of the 100 myelograms in this series were interpreted as normal and in 3 instances these proved to be accurate, as the findings at operation were also negative. In the other 9 cases pathologic disks were found. In one patient with a myelographic defect no abnormal disk was found. Among the 88 patients with positive myelograms, 19 were found to have slight defects, consisting either of obliterated root sleeves or small indentations in the dural sac. In 47 cases there were definite unilateral indentations, in 20 mid-line or hourglass deformities, and in 2 such large ruptures that complete blocks were present.

In 11 cases the decision to operate was based solely on the myelogram. In the remaining 89 cases, surgery would have been performed regardless of the myelographic findings.

The overall accuracy of the myelogram was found to be only 60 per cent. In 12 cases there were relatively unimportant discrepancies, but in 28 cases major discrepancies were found. The authors believe that a negative myelogram should not contraindicate the per-

formance of disk surgery when symptoms and physical findings indicate operation; nor is it necessary to subject a patient to myelography when the history, clinical course, and physical findings definitely indicate a disk lesion and the surgeon is able to determine the approximate location of the abnormal disk.

HOWARD L. STEINBACH, M.D.
University of California

Herniated Cervical Disc. A New Form of Traction Therapy. Bernard D. Judovich. *Am. J. Surg.* 84: 646-656, December 1952.

Pain in the shoulder girdle due to a herniated cervical disk must be differentiated from similar pain as a result of (1) local processes, (2) vascular disease, (3) peripheral nerve disease, (4) brachial plexus disease, (5) root affections, (6) intramedullary spinal cord lesions, (7) referred pain and (8) psychalgia. As a part of the routine work-up, x-rays of the cervical and dorsal spine, chest, shoulder joint, and scapula are included. Myelograms are obtained in selected cases.

A detailed review of the symptoms and clinical findings in cervical disk herniation is given. It is pointed out that in the lateral view of the cervical spine the intervertebral space may or may not be narrowed. The one most significant sign in differential diagnosis was the increase of the pain on spinal cord compression and flexion of the neck toward the affected side, and lessening or complete relief of pain by means of spinal traction. In 60 cases test traction was applied by use of a head halter and the application of increasing force, 5 pounds at a time, up to 45 or 50 pounds. With sufficient force, relief was obtained in almost half the patients. The minimum effective amount was 25 to 30 pounds. Roentgenograms of the lateral cervical spine were made with successive additions of traction in 7 patients. In 6 of these, the earliest measurable change was noted at 25 pounds of traction. Measurements were made from the inferior surface of C2 to the upper surface of C7. At 45 pounds of traction an average separation of 5 mm. was noted with a range of from 3 to 14 mm. In 6 of the 7 patients a perceptible widening of the apophyseal joints was noted, averaging 2 to 3 mm. The curve of the cervical spine straightened at 20 to 25 pounds of traction.

An outline of the management of an average case is given and is supplemented with 7 detailed case reports. A description of the motorized intermittent traction device and its application is included.

Two roentgenograms; 3 photographs.

GEORGE A. SHIPMAN, M.D.
New Orleans, La.

Diskography in Ankylosing Spondylitis. Ragnar Romanus and Sven Ydén. *Acta radiol.* 38: 431-439, December 1952.

While it has been generally considered characteristic of ankylosing spondylitis that the intervertebral disks remain normal, it has been pointed out in recent years that diminution of the intervertebral space may occur in this disease. Having observed such space narrowing in the course of observations in a series of 110 men with objective signs of ankylosing spondylitis, the authors undertook diskography in 30 of the number. One to three of the lower lumbar disks, amounting to 74 in all, were investigated. Of these, 39 were found to be normal, while 35 showed pathological changes. Of the latter, 29 are described as of the "usual" type and 6 as

showing the appearances of a typical rupture. In these 6 cases, reported in some detail, injection of the contrast medium served to reproduce the type of pain already suffered by the patient, indicating that it had its origin in the degenerated disk. The presence of a ruptured disk giving rise to symptoms in a patient with ankylosing spondylitis will greatly alter the treatment. This complication should be suspected in all patients complaining of pain predominantly of the sciatic or lumbago type.

The authors describe in detail the method they used for injection of the contrast medium, with a thin puncture needle inserted into the center of the disk under fluoroscopic control.

Ten roentgenograms. A. WILSON BROWN, M.D.
Shreveport, La.

Roentgen Examination of Bennett's Fracture. Lars Billing and K.-O. Gedda. *Acta radiol.* **38**: 471-476, December 1952.

The authors point out the necessity of a true lateral view of the carpo-metacarpal joint of the thumb for examining and treating a Bennett's fracture. In such a view the first carpo-metacarpal joint is projected over the base of the second metacarpal bone and the greater and lesser multiangular bones are superimposed. To obtain a true lateral view, a simple apparatus for the fixation of the hand has been devised. This apparatus facilitates positioning and makes it possible to carry out accurate repeat examinations. The report is based on experience with examinations of both hands in more than 100 cases.

Seventeen roentgenograms; 2 drawings; 2 photographs. A. J. NICHOLAS, M.D.
Shreveport, La.

THE GENITOURINARY SYSTEM

Presacral Insufflation of Oxygen for Outlining the Contents of the Retroperitoneal Space. Lionel Reese and John T. MacLean. *Canad. M. A. J.* **67**: 632-637, December 1952.

Presacral air insufflation is often of great value in clarifying the diagnosis in urologic cases that remain obscure after detailed investigation by other means. The authors use a modification of the method developed by Ruiz Rivas (*Rev. clin. españ.* **25**: 206, 1947). With the patient in the knee-chest position, the needle is inserted beneath the tip of the coccyx and advanced 4 cm. along the mid-line in a superior and posterior direction, following the hollow of the sacrum. A syringe is then attached and the needle is rotated through a complete cycle while constant aspiration is maintained to make certain that a blood vessel has not been entered. If blood should be aspirated the position of the needle must be changed. The needle is connected to an oxygen supply and a syringe through a three-way stopcock and length of rubber tubing. A cotton filter intervenes between the oxygen tank and syringe to eliminate any foreign matter. The syringe is filled with an intermittent flow of oxygen. Each 50 c.c. is injected slowly. At first a sense of resistance to the injection is felt, but after 100 c.c. or so, the resistance gives way and the injection is effortless. Between 1,000 and 1,500 c.c. of oxygen are injected, depending upon the size of the patient. On completion of the injection, the patient is turned on his back and made to sit up and lie down ten times, to insure diffusion of the oxygen. A flat plate is

taken to determine the state of diffusion, followed by an intravenous pyelogram series or cystoscopy with retrograde pyelography.

The authors also give the details of Rivas' original technic and of Blackwood's modification (*Brit. J. Surg.* **39**: 111, 1951. *Abst. in Radiology* **59**: 294, 1952).

Only one complication has been noted in 20 presacral insufflations. In that case surgical emphysema extending up to the neck developed. This was absorbed in twenty-four hours without treatment except for aspirin and codeine for the relief of the discomfort. Almost all the patients complain of a feeling of distention, but this soon passes off. About half the patients have complained of transient pain in the tip of the shoulder, which is due to diaphragmatic irritation.

Four brief case reports are included.

Six roentgenograms; 2 drawings.

JOHN M. KOHL, M.D.
Jefferson Hospital

A New Instrument for Urethrocytography. Lennart Kjellman. *Acta radiol.* **38**: 440-446, December 1952.

The method most commonly employed for the radiographic examination of the female bladder and urethra, carried out after filling of the bladder with contrast medium by catheterization, gives a clear picture of any bladder changes but fails to furnish sufficient information as to the mucosal pattern of the urethra. The great difficulty in retrograde urethrocytography lies in the fact that it is often not possible to prevent leakage at the urethral orifice in injecting the contrast material, and that efforts to avoid this by pressure may cause an undesirable shortening and deformation of the lumen. The author believes that he has solved this problem by use of the suction principle. The instrument which he has devised consists of a straight, in part double-barrelled, cannula of stainless steel, one end of which has a connection for a syringe and a tap. Near this end, projecting at an angle, is a short tube the lumen of which emerges at the base of a rubber olive attached to the other end of the cannula. Both the cone and the orifice of the tube are enclosed in a two-piece bell of transparent acrylic plastic material. The projecting tube is coupled to a water suction plant and the tip of the olive is introduced into the urethral orifice. The instrument will adhere to the surrounding mucous membrane once the movable plastic cap has been adjusted by means of an expanding screw, which also closes the gap between the bell and the cannula. When enough soft tissue has been drawn up around the rubber cone, the latter should be pushed slightly forward. The tissue will then act as a tampon and increase the effect of the suction.

This instrument can be used to advantage in the male as well as in the female, and with slight modification in children.

Nine roentgenograms; 1 photograph showing the instrument assembled and its component parts.

A. WILSON BROWN, M.D.
Shreveport, La.

Divided Ureter: A Rare Congenital Anomaly. Enrico Lattanzio. *Radiol. med. (Milan)* **38**: 921-928, October 1952. (In Italian)

The author presents two cases in which one of the ureters, after originating as a single tube from the kidney pelvis, became double in its pelvic portion. In a third case there was doubling of the ureter in its lumbar

portion. A fourth patient presented a diverticulum of the ureter in the lumbar area followed by doubling in the pelvic portion. These anomalies are said to be exceptionally rare. They have not been previously described in the radiological literature.

Ten roentgenograms. **CESARE GIANTURCO, M.D.**
Urbana, Ill.

Perivesical Bleeding Following Herniorrhaphy Demonstrated by Cystography. Garfield L. Suder. *Surgery* 32: 988-990, December 1952.

A case demonstrating "teardrop" deformity of the bladder following herniorrhaphy is reported. Twenty-four hours after operation the patient complained of mild periumbilical pain which persisted for forty-eight hours. On the fourth postoperative night, the pain increased in severity and shifted to the left lower quadrant. It was accompanied by anorexia and fever, and tenderness, spasm, and rebound tenderness in the left lower quadrant. A cystogram revealed a teardrop deformity of the bladder. On the eleventh postoperative day, the cystogram was repeated and the contour of the bladder was found to be normal. One month later the cystogram was still normal with the exception of elevation of the right side, which was the site of operation.

The deformity of the bladder was thought to be due to bleeding in the perivesical space.

Three roentgenograms.

HOWARD L. STEINBACH, M.D.
University of California

Radiology in Diseases of the Prostate. J. H. Middlemiss. *J. Fac. Radiologists* 4: 115-124, October 1952.

In assessing the place of radiology relative to disease of the prostate, plain radiography, excretory urography, and cysto-urethrography as described by Waldron (*J. Fac. Radiologists* 4: 54, 1952. *Abst. in Radiology* 60: 782, 1953) are considered. By means of these techniques, many pathological as well as postoperative conditions can be demonstrated. Among these are prostatic calculi, adenomatous enlargement of the prostate, and prostatic carcinoma. In addition, the effect of prostatic disease on the remainder of the urinary tract can be comprehensively and specifically studied.

Each of the conditions mentioned above is discussed, representative roentgenograms are reproduced, and problems of differential diagnosis are considered.

Plain radiography will allow evaluation of prostatic calculi, calculi in the prostatic urethra from the kidney or bladder, and calcification related to chronic prostatitis. Examination of the skeleton for metastatic lesions is a most important aspect when dealing with malignant disease. Osteitis pubis is occasionally seen.

Contrast studies aid considerably in many phases of prostatic disease. Cysto-urethrography may demonstrate post-inflammatory changes such as fistulae and strictures or aid in evaluation of post-prostatectomy problems of incontinence or obstruction. Abnormal fixation and rigidity of the posterior urethra without normal dilatation on micturition may be observed with prostatic carcinoma.

In some normal cases, the contrast-filled bladder may show an inter-ureteric bar, the internal urinary meatus, or a filling defect produced by gas in the sigmoid. By tilting the x-ray tube 5° toward the head and centering

it 0.5 inch below the symphysis, with the patient erect, one may better evaluate these findings. Oblique views may also be necessary.

Prostatic enlargement may cause filling defects and elevation of the bladder base or lateral deviation with lengthening and forward angulation of the supracolic portion of the urethra. Multiple papillomata or neoplasms usually produce "off-center" filling defects, not at the base.

Prostatic disease may reflect its effect on the bladder by producing retention of urine and hypertrophy, trabeculation, saccululation, dilatation, and diverticula. Similar functional impairment and physiological changes may be demonstrable in the ureters and kidneys.

In conclusion, two points are stressed: (1) the role of the radiologist in giving the surgeon the "all-clear" in the upper urinary tract and sounding the "warning bell" about possible disease in the lower tract; (2) the complementary roles of clinical and radiological examinations.

Thirty-four roentgenograms.

EDWARD E. TENNANT, M.D.
Jacksonville, N. C.

Radiology in Diseases of the Prostate. Ashton Miller. *J. Fac. Radiologists* 4: 125-129, October 1952.

Radiology aids the clinical urologist in diseases of the prostate primarily with respect to hypertrophy and carcinoma of the gland.

Intravenous pyelography forms part of the routine investigation and assessment of all patients with symptoms of prostatic enlargement, since clinical examination reveals only the gross abnormality. The pyelogram serves as an excellent renal function test; it reveals or rules out complications in the kidneys, ureters, and bladder; it permits estimation of residual urine without instrumentation.

These observations are equally applicable in carcinomatous obstruction, though the "educated finger" is still the best method of diagnosing carcinoma of the prostate.

Cystourethrography is most useful when, in a patient with post-prostatectomy obstruction, it is impossible to introduce a urethral instrument.

Eleven roentgenograms.

EDWARD E. TENNANT, M.D.
Jacksonville, N. C.

THE BLOOD VESSELS

Chronic Obstruction of the Abdominal Aorta. Report of 30 Cases. Bernardo Milanés, Rodrigo Bustamante, Roberto Guerra, Armando Núñez Núñez, Alfredo L. Hernandez, Eliseo Pérez-Stable, Jorge McCook, and Juan Rodríguez Iñigo. *Angiology* 3: 472-482, December 1952.

Among 4,560 patients seen in the last four years in the Department of Vascular Diseases of the Havana University Hospital and in private practice, the authors have been able to confirm the diagnosis of chronic obstruction of the abdominal aorta (Leriche syndrome) in 25 men (20 white, 5 Negroes) and 5 women (4 white, 1 Negro). Early symptoms consisted of coldness and easy fatigability along with weakness of the lower limbs on walking; later symptomatology depends upon the condition of the collateral circulation.

Physical findings which were constantly observed in

the authors' series were (1) absence of pulsations and oscillations in both lower extremities, (2) absence or greatly diminished pulsation in both iliac arteries and infra-umbilical segment of the aorta, (3) muscular atrophy with loss of hair of the lower limbs, and more or less marked discoloration. While the clinical symptoms and physical signs are nearly always sufficient to be diagnostic, bilateral obstruction of the iliac arteries may produce an identical picture. Translumbar aortography not only establishes the diagnosis but yields at the same time important information concerning the extension of the thrombotic process and the state of the collateral circulation, both of which bear a direct relationship to prognosis and treatment.

Treatment of the Leriche syndrome is discouraging. In the stage of compensated obliteration, medical management was used in 12 cases with little or no improvement. Lumbar sympathectomy was performed in 17 cases, in 5 of them combined with aortoiliac resection; varying degrees of improvement followed in 8 cases but no difference could be observed in the long-term results obtained with sympathectomy alone and associated with aortoiliac resection. Endarterectomy was done in one case and the patient died three days after operation from retroperitoneal hemorrhage caused by a leakage at the line of suture of the artery. Nevertheless, the authors believe that the only possibility of real improvement in chronic obstruction of the abdominal aorta depends on such advanced surgical procedures as endarterectomy or vessel grafting.

Four of the more interesting cases are presented in detail.

Five roentgenograms; 2 photographs; 3 tables.

Two Cases of Venous Stasis. Radiological Findings.

G. S. Andrews and M. Denny. South African M. J. 26: 729-732, Sept. 6, 1952.

The authors analyze 2 cases of venous stasis with particular reference to the radiological findings. Conventional radiographs were supplemented by venography to demonstrate the vascular pathology.

One case represented an anomaly of the venous system as evidenced by soft-tissue swelling, vascular calcification, initial sclerotic and then proliferative bony change representing the result of pressure erosion. Diodrast was injected into a dilated vein on the dorsum of the hand, revealing dilated, tortuous vessels with a large thrombus in the basilic vein.

The second case represented venous stasis secondary to mediastinal compression. The cause in this instance was not determined, although a positive Wassermann reaction and fluoroscopy suggested syphilitic involvement of the aorta. Diodrast was injected into a vein in the arm. Obstruction was encountered at the commencement of the right innominate vein, extending into the superior vena cava as far as its entry into the pericardium. The vena azygos major acted as a collateral channel, as it sometimes does in the presence of obstructive lesions.

Although, as suggested above, a syphilitic etiology was suspected in this latter case, the fact that primary or secondary malignant thoracic tumors account for from 33 to 78 per cent of cases of superior vena caval obstruction had also to be taken into consideration. A final diagnosis was not obtained.

Eight roentgenograms; 1 photograph.

ROBERT H. LEAMING, M.D.
Memorial Center, N. Y.

TECHNIC

Measurement of Tissue Components Radiologically.

Frank Falkner and Sylvia Wisdom. Brit. M. J. 2: 1240-1241, Dec. 6, 1952.

A method of obtaining measurements of soft-tissue thicknesses and bone in the course of growth studies is presented. It involves simultaneous exposures of the part to be examined by two x-ray tubes separated by a known distance in a plane parallel to the film. An overlapping double image is produced and corrections for magnification are obtained from the amount of separation of the images.

One must first construct a graph by using objects at varying known distances and charting the amounts the images are separated. [Then the tissue in question need not be at a certain fixed distance from the film.—Z.F.E.] When the part-film distance is obtained, the corrected thickness is easily derived by using the thickness measured on the film and the known distances of tube-to-film and part-to-film in the formula $X = \frac{X^1(K-d)}{K}$ where X = true size, X^1 = the size of the

image on the film, K = tube-to-film distance, and d = part-to-film distance.

[A reproduction of the graph and an example would have made the description of the method much clearer.]

Two drawings. ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Investigations on the Optimal Illumination of Viewing Cabinets.

Bjarne Merrild-Hansen and Erling Ratjen. Acta radiol. 38: 447-460, December 1952.

This is an exhaustive article on the subject of optimal illumination of viewing cabinets. The authors stress the importance of two factors in diagnostic radiology: the production of a technically satisfactory radiograph and its interpretation. Visual impressions are based on two fundamental qualities of the visual senses: (1) the power to apprehend light and (2) the resolving power of the eye.

There is considerable discussion of the various methods used in reaching conclusions as to the optimal amount of illumination necessary in viewing cabinets, as well as of the various types of light available for use in roentgenographic interpretation—daylight, incandescent light, and fluorescent tubes. A complete survey of the principles and the physiologic basis for viewing of roentgen films is given.

As far as may be gathered from the literature, no special color of light is to be preferred. On the basis of experiments on test films, the authors suggest a viewing box brightness of about 200 to 1,000 foot-lamberts. Glare is of no practical importance in the younger age groups. The risk of erroneous diagnosis is considered greater with a dim than a strong light. For the time being, fluorescent tubes are considered the most suitable sources of light.

Eight figures. A. WILSON BROWN, M.D.
Shreveport, La.

Aspects of the Interpretation of Contrast and Detail in Radiographs.

Ove Mattsson. Acta radiol. 38: 477-488, December 1952.

The author discusses the photographic, physiologic, and optical factors influencing the interpretation of detail and contrast in radiographs, especially those

heavily exposed. The importance of reflection from the film surface is pointed out. The general opinion is that a strong small source of light should be used for the best evaluation of the denser film detail, though the error of this conception has been pointed out by Spiegler (Fortschr. a. d. Geb. d. Röntgenstrahlen 53: 678, 1936) and Bergerhoff (Röntgenpraxis 17: 244, 1948).

A simple viewing device which eliminates reflection and produces optimal functional conditions for the eyes is described.

Two photographs; 4 graphs.

A. J. NICHOLAS, M.D.
Shreveport, La.

The Use of Ultraviolet-Microscopy, Roentgen-Ray Absorption, and Radioautographic Techniques in the Study of Neoplastic Disease. A Discussion of These Cytophysical Techniques. Patrick J. Fitzgerald and Arne Engstrom. *Cancer* 5: 643-677, July 1952.

In recent years three new cytophysical techniques, using radiant energy, have been applied to thin histologic sections in an attempt to determine certain chemical and physical properties of cells and organs, namely ultraviolet microscopy, roentgen-ray absorption, and radioautography. These the authors review in great detail, with abundant citations from the literature (their bibliography includes 257 references). An adequate

abstract of the paper is quite impossible. It includes the preparation of the biological materials, problems in the specificity of the information obtainable by the procedures, the interpretation of results, and future possibilities of the methods.

In general, cytophysical techniques are "sensitive," *i.e.*, they permit the determination of very small amounts of a substance. In many cases, however, the substance must be present in relatively high concentration. This is an important feature of the radiation absorption technic. Radioautography, with its ability to detect individual particle tracks, has an extremely high sensitivity, it having been estimated that as few as 100 atoms of P^{32} may be detected by this means.

In comparison with macrochemical methods, the accuracy of cytochemical determinations is low. However, biological variation is large, and in order to solve the many biological problems in which differences are great, it is not necessary to work with so high a degree of precision. In each case, nevertheless, an estimate of the error involved must be made in order to indicate to what extent the conclusions drawn are valid.

Properly used in well defined problems, the cytophysical techniques may give new and valuable information as to the composition and function of normal and malignant cells.

Twenty-four illustrations.

RADIOTHERAPY

Radiotherapy of Diseases of the Cornea. M. Lederman. *J. Fac. Radiologists* 4: 97-114, October 1952.

In disease of the eye radiation should be regarded as an additional therapeutic aid in patients who fail to respond to orthodox treatment. In non-neoplastic disease it may relieve pain, promote healing, and reduce congestion and corneal edema. In neoplasms, except for epithelioma of the limbus, radiotherapy has little to offer.

Factors which increase the corneal reaction to radiation include high dosage, large fields including the bulbar conjunctiva and lids, pathological processes within the cornea itself, and trauma or infection incurred during therapy. The two latter are the great dangers.

A number of technics are available for the treatment of benign lesions:

(1) "Whole eye" roentgen irradiation, given through a field 3 cm. in diameter over the closed lids, with the following factors: 45 kv., 2 ma., 1 mm. Al filtration, 4 cm. F.S.D. Applicable to acute inflammatory conditions, with doses of 10 to 20 r once or twice weekly for four to six weeks.

(2) Corneal roentgen technic, utilizing a special applicator which restricts the beam to the cornea and anterior chamber. Factors: 100 kv., 5 ma., 0.1-mm. Cu filter, F.D.S. 28 cm., field 2 X 1 cm. Applicable to all inflammatory lesions and corneal ulcerations other than Mooren's ulcer, and, with modifications of dosage, for devascularizing the cornea (200 r weekly for four weeks) and for pterygium (600 r in five days).

(3) Anterior segment roentgen technic, with same apparatus, factors, and dosage as the corneal technic, but with the applicator placed on the closed eye so that the beam is directed to the lids, conjunctival sac, and anterior chamber. Useful for keratitis complicated by a conjunctivitis or blepharitis and for repeated courses as an alternative to the "whole eye" technic.

(4) Beta radiation from radium or P^{32} for single doses of 400 to 1,000 r. Indicated for localized corneal ulceration and vascularized scars, for devascularization before corneal grafting, and as a supplement to x-ray therapy in chronic forms of keratitis with ulceration or vascularization; not to be used in acute cases.

Treatment of malignant limbal epithelioma involves separation of the lids by a speculum and irradiation through a suitably sized field. Low-voltage x-rays may be used with treatments of 400 r, so as to deliver 6,000 r in three weeks. The possibility of lens damage must be accepted. Radon seed implantation may be used post-operatively following excision of a conjunctival or limbal melanoma. Tying the seeds in place for a dose of 3,000 to 4,000 r in three to four days is advised.

The overall results of treatment in 146 cases of benign lesions showed successful response of the lesion in 55, slight improvement in 64, and no benefit in 29. Rosacea keratitis responded best to early treatment, which prevented corneal damage. Treatment for superficial punctate keratitis was not as effective and should not be as intensive. The only hope of cure for Mooren's ulcer lies in radiotherapy. Beta radiation is advised, as in all types of corneal ulcers. Preoperative treatment of corneal vascularization is considered advisable only in cases where the cornea is heavily vascularized. The ideal method of treatment in such cases is postoperative irradiation, preferably using x-rays. Treatment should be instituted within seven to ten days after surgery unless the eye is too irritable. Therapy may be tried in cases of late opacification of the graft.

Radiotherapy is considered the treatment of choice for limbal epithelioma. Excellent results were obtained in 5 cases.

Twenty-five illustrations; 5 tables.

EDWARD E. TENNANT, M.D.
Jacksonville, N. C.

Retinoblastoma Successfully Treated with X-Rays: Normal Vision Retained After Thirty-four Years. Second Report on a Case. F. H. Verhoeff. *Arch. Ophth.* 48: 720-722, December 1952.

The author presents a second report on a case of retinoblastoma treated by x-rays in 1918 (see Verhoeff: *Arch. Ophth.* 50: 450, 1921). The patient was first seen in 1917, at the age of seventeen months. The right eye was removed and found to be largely involved by a retinoblastoma, containing many rosettes. The tumor had not invaded the optic nerve or choroid. About six months following surgery there was found in the retina of the left eye a white opaque elevated mass, irregularly oval in shape. Near this mass, but entirely separate from it, were two small white spots. The patient was referred for x-ray therapy to the left eye. A suberythema dose through a 5-mm. aluminum filter was administered at weekly intervals for four treatments and five other times at longer intervals over the next six months. In 1921, the tumor appeared smaller than when originally seen, only slightly elevated, gray and translucent. No trace of the white spots could be found. The lens was clear. The patient was last seen in 1952, when he was nearly thirty-six years of age, thirty-four years after the first x-ray treatment. His general health was excellent. The tumor site and the posterior cortical cataract were unchanged in appearance. Vision in the left eye was 20/30+.

The question of whether this case is an example of spontaneous regression of a retinoblastoma is discussed.

Carcinoma of the Tongue. John L. Wilson and Louis G. Brizzolara. *Ann. Surg.* 136: 964-970, December 1952.

A series of 54 cases of tongue cancer treated more than five years ago is reported, using the classification which was introduced in 1939 by W. L. Harnett, Medical Secretary to the clinical Cancer Research Committee of the British Empire Cancer Campaign, as follows:

- Stage I: Confined to organ of origin.
- Stage II: Adjacent tissue invaded but lymph nodes not involved.
- Stage III: Lymph nodes invaded.
 - A. Adjacent tissues not invaded.
 - B. Adjacent tissues invaded.
- Stage IV: Remote metastases present.

The authors believe this system has the virtues of simplicity and ready clinical applicability. In addition it takes account of the broad prognostic implications of local extent and metastatic spread of the disease without resorting to complicated subdivision and unwarranted refinement of grouping based on small differences in lesion size. All presented cases are fitted into this classification.

Twenty-five cases were of Stage I, and in 20 of these roentgen therapy was used, either alone or in combination with radium. The five-year survival rate in this group, based on 21 "determinate cases", was 57 per cent. Of 14 patients treated by roentgen rays alone, 6 survived five years. Stage II cases numbered 6, with a single five-year survival. None of the patients treated by irradiation lived for five years. Twenty-three cases with lymph node involvement (Stage III) were treated. There are many reports of patients in this stage treated by irradiation of the primary lesion and node dissection, but the authors have had but little success with this

approach. Only 1 of their 23 patients lived five years. Palliative measures alone are applicable in Stage IV.

Four figures; 5 tables.

JOSEPH P. TOMSULA, M.D.
Baton Rouge, La.

Regression of Metastatic Lesions of Breast Carcinoma Following Sterilization. Richard A. Ellis and Harold G. Scheie. *Arch. Ophth.* 48: 455-459, October 1952.

The authors report 2 cases of carcinoma of the breast with metastases. In both cases lung metastases cleared, and in 1 case metastatic lesions in the choroid of both eyes showed decided improvement after sterilization by x-rays. To the best of the authors' knowledge, the latter observation has not been recorded previously.

Four roentgenograms; 1 graph.

Seven-Year Survival After Radiation Therapy in a Patient with Inoperable Cancer of the Lung. Harry W. Burnett, Jr., Israel Steinberg, and Charles T. Dotter. *New England J. Med.* 247: 850-851, Nov. 27, 1952.

A well-documented case report of a 42-year-old man with microscopically proved bronchogenic carcinoma in an inoperable stage is presented. Survival for seven years is of interest to those who question whether palliative deep therapy is justifiable.

This man had smoked ten cigarettes or more daily for twenty years. He complained of cough and a loss of weight (25 pounds in two months). Roentgen examination, bronchoscopy, and biopsy established the diagnosis. Exploratory thoracotomy showed the lesion to be unresectable. Deep therapy through two anterior and two posterior chest portals (14 × 7 cm.) was given at 250 kv. with 1.4 mm. copper half-value layer. The target-skin distance was 70 cm. Dosage was 300 r in air to each of two portals daily for a total of 3,000 r in air to each portal. The calculated skin dose was 3,900 r, calculated tumor dose 3,840 r.

For seven years after therapy the patient suffered no unusual symptoms other than a chronic non-productive cough. In view of this result, the authors believe that x-ray treatment of cancer of the lung should be regarded as more than a palliative measure.

Two roentgenograms; 1 photomicrograph.

DONALD DEF. BAUER, M.D.
Coos Bay, Ore.

Clinical Results Following Different Methods of Radium Application Used in the Treatment of Cervical Cancer from 1921 to 1947. MacDonald Bonebrake, Alfred I. Sherman, Michel Ter-Pogossian, and A. Norman Arneson. *Am. J. Roentgenol.* 68: 925-934, December 1952.

The authors have evaluated 490 cases of carcinoma of the cervix treated at the Washington University School of Medicine (St. Louis) from 1921 to 1947. The cases were studied on the basis of method of treatment, complications, and survival rates.

Three major treatment groups are included:

I. From 1921 to 1931 treatment was almost entirely by radium. A high-intensity tandem of 75 to 100 mg. was placed in the uterine canal, and no vaginal radium sources were used. The uterine end of the tandem contained 25 mg. and the cervical 75 mg. The average total dose was 3,000 mg. hours at one application. By reconstruction of this method and use of a scintillation

counter, the dosage to points A and B and the rectum and bladder have been determined. The average values were 5,000 gamma r, 1,000 gamma r, 12,200 gamma r, and 10,700 gamma r, respectively. This method, then, produced low dosage at point B, and in many cases doses exceeding tolerance in the rectum and bladder. There was a 10 per cent incidence of bladder complications and a 35 per cent incidence of rectal complications.

II. The next method of treatment, from 1932 to 1936, consisted of a rearrangement of the radium in the tandem, so that each end contained 50 mg., with 0.2 mm. platinum filter. These patients received 5,000 mg. hours. The doses at points A and B, and to rectum and bladder were 7,000 gamma r, 1,500 gamma r, 9,800 gamma r, and 8,300 gamma r. The number of complications decreased 3 per cent.

III. Vaginal radium applications were added to the treatment in 1937. Three 25-mg. cells were used in the cervical canal and a 25-mg. cell embedded in sponge rubber in each lateral fornix. The patients received from 4,000 to 5,500 mg. hours, initially at a single sitting but later at two treatment sessions. The doses to points A and B and to rectum and bladder were 7,000 gamma r, 1,900 gamma r, 7,400 gamma r, and 6,700 gamma r. This group of patients also had a tumor dose of 1,500 r by external irradiation, and in some instances, 3,000-5,000 r were added by intravaginal irradiation. The technic of external and intravaginal irradiation is not given. The incidence of complications in this group is half of that of the preceding period.

The authors' present method is a modification of the above outline. They now use 20 mg. of radium in each fornix, 5 mg. at the cervical end of the tandem and 10 mg. in the middle and upper uterine segments, with total doses of 7,000 to 8,000 mg. hours. External irradiation has been increased, with use of higher doses and smaller portals, although the technic is not described.

The complications are considered as any reasonable evidence of irradiation reaction, such as fever, diarrhea, rectal bleeding, urinary distress, or definite local reaction in the rectum or bladder. Infection and complications are closely related. In the authors' series, of those patients having complications, 66 per cent showed infection on the initial visit. Only 18 per cent of the non-infected patients had complications.

Complications are also related to the gross morphology of the tumor. They were encountered in only 27 per cent of fungating lesions but in 46 per cent of the infiltrating and 42 per cent of the ulcerating lesions.

The classification has been that of the League of Nations. The article contains numerous tables and drawings clearly showing the relationship to method of treatment, survival rates, and complications. The improvement in survival rates and reduction of complications is attributed to better radium distribution, a lower intensity of irradiation, and increase in treatment time.

Two photomicrographs; 5 drawings; 1 photograph; 5 tables.

M. HARLAN JOHNSTON, M.D.
Jacksonville, Fla.

A Physical Approach to the Design of Applicators in Radium Therapy of Cancer of the Cervix Uteri. Gilbert H. Fletcher, Robert J. Shalek, John A. Wall, and Fernando G. Bloedorn. *Am. J. Roentgenol.* 68: 935-947, December 1952.

In the experience of the authors, direct measurements

in the rectum and bladder with a scintillation counter probe have proved of practical value in radium therapy of carcinoma of the cervix.

They have designed a colpostat (see *Radiology* 60: 77, 1953) which consists of a primary unit of stainless steel or brass attached to interlocking handles. Plastic ovoids of varying sizes may be placed over the primary colpostat to give an applicator up to 3.0 cm. in diameter. In the ends of the primary colpostat tungsten buttons are used to reduce irradiation in the direction of the rectum and bladder. Treatment consists of two applications of seventy-two hours each, the tandem and ovoids being used at the same time, if possible. Radium therapy is given prior to external irradiation when possible, to take advantage of the size of the vaginal vault. Modifications of the radium application are made depending on the clinical variety, stage of the disease, and position of the uterus. The ovoids and tandems are loaded according to the Manchester system.

The direct measurements with a scintillation counter are made (1) in the rectum and bladder after the tandem has been inserted, (2) in the bladder, anterior and posterior fornices, and rectum after placing the loaded ovoids and before packing, and (3) in the rectum after packing. The counter probe, graduated in centimeters, is inserted in the bladder and rectum and readings are taken at every centimeter, both on insertion and withdrawal. Tight packing helps to displace the whole radium system upward and centrally and thus reduce the dosage to the rectum and bladder and gives a better contribution to the pelvic nodes.

Roentgenograms are obtained after the application, with sodium iodide in the bulb of a Foley catheter in the bladder and barium in the rectum. By the method of LaTouche and Spiers (*Brit. J. Radiol.* 13: 314, 1940. *Abst. in Radiology* 37: 120, 1941), dosage is calculated at the following points: base of the bladder, anterior wall of the rectum, the posterior fornix, points A and B, the obturator nodes, and the hypogastric nodes. The determination of the contribution from the tandem and each ovoid to each of these points is then made. The loading of the tandem and each ovoid is modified for subsequent implantation according to the contribution of the various sources.

Up to the present, the authors had done direct scintillation measurements on 40 cases and both measurements and calculation in 30 cases. These measurements and calculations are only approximate because of the steep gradient of intensity in the vicinity of the radium sources. A slight difference in pressure on the base of the bladder or anterior wall of the rectum results in an appreciable difference. Varying anatomy and changes as a result of disease preclude a table of dosages for the entire system.

It has been found that the tandem contributes most to the bladder dose and this may be very high in the presence of marked antelexion. The dosage to the rectum from the colpostats is low, and packing between the colpostats and rectovaginal septum has seldom been necessary.

Direct measurements in this system have shown that the bladder and rectum tolerance is a function of the size of the area of high dosage.

Using these methods, one should be able to correlate dosage and complications on an experimental basis.

Three roentgenograms; 5 photographs; 2 tables; 1 drawing.

M. HARLAN JOHNSTON, M.D.
Jacksonville, Fla.

Radiation Therapy in Menstrual Disorders and Sterility. L. D. Bonar and R. L. Garber. *Am. J. Obst. & Gynec.* 64: 1350-1354, December 1952.

In an effort to obtain information as to the value of low-dosage radiation therapy for menstrual disturbances and sterility, a series of 39 patients was studied. Eight patients had menstrual irregularity only and 31 presented sterility problems. The average period of infertility was five years and the extremes were two to ten years.

Both the pituitary gland and the ovarian regions were irradiated. Each area received a total of 150 r (in air) over a two-week period, with the following factors: 200 kv., 0.5 mm. Cu and 1.0 mm. Al filtration, 50 cm. skin-target distance, 20 ma. A 5-cm. diameter field was used over each lateral pituitary region and 10 X 10-cm. or 10 X 15-cm. portals for the anterior and posterior ovarian regions.

Results were considered satisfactory in 7 of the 8 patients with menstrual disorders. Fourteen of the patients having sterility problems had subsequent pregnancies. Four patients were delivered of a second child, making a total of 17 infants born. Biopsies of the endometrium were taken before and after therapy. The changes noted are discussed.

No demonstrable abnormality has been found in any of the infants.

Four photomicrographs. JOHN M. KOHL, M.D.
Jefferson Medical College

Antroduodenectomy and X-ray Irradiation in the Treatment of Duodenal Ulcer. Grayton Brown, R. Kaye Scott, W. P. Holman, I. J. Wood, E. S. Finckh, S. Weiden, and P. Davis. *Lancet* 2: 1145-1149, Dec. 13, 1952.

Following the example of Ricketts, Palmer, *et al.* (*Gastroenterology* 11: 789, 807, 1949. *Abst. in Radiology* 53: 776, 777, 1949), the authors undertook the treatment of duodenal ulcer by roentgen rays. The technic found to give the best results called for a dose of 2,000 r during three weeks (technical factors not stated), through a small port accurately centered over the stomach. Serial histamine test meals after irradiation revealed a decrease in the volume of secretion and in the concentration of free acid and pepsin, with return to pre-irradiation levels after six months or more. A single course of treatment usually produced immediate and complete remission of symptoms, but in 4 of the 10 cases treated, severe relapses occurred after intervals of eight, twelve, twelve, and twenty-five months, respectively.

In view of these disappointing results, it was decided to combine local excision of the ulcer-bearing portion of the duodenum and gastric antrum with irradiation to reduce the secretion of acid and pepsin. In 2 cases irradiation was done prior to operation and in 10 cases two months afterward. Early results are encouraging, but the follow-up periods are brief. The authors predict, however, a higher proportion of satisfactory results from this form of treatment than from other methods, "for it is reasonable to expect that, with the excision of the vulnerable antrum and first part of the duodenum, and with the suppression of acid and pepsin secretion by irradiation for six to twelve months, the body of the stomach and the second part of the duodenum will remain free from ulceration."

Six illustrations.

Combined Nitrogen Mustard and Single Dose Irradiation Treatment of Lymphomata and Other Malignant Tumors. Leslie W. Rose, Jr., H. St. George Tucker, Jr., Samuel Richman, and John P. Williams. *Virginia M. Monthly* 79: 562-574, October 1952.

The authors report their observations on a series of 52 patients with advanced lymphomata and other neoplasms who were subjected to a combination of nitrogen mustard and single dose irradiation. Their object was to summate the diffuse effect of nitrogen mustard with the localized effect of irradiation.

All 52 cases were proved histologically. The nitrogen mustard, 0.3 mg./kg. of body weight, was injected over a two-minute period into the tubing of a running saline intravenous infusion apparatus. The patient was then sent immediately to the X-Ray Department, where irradiation was directed to one or more tumor sites. The physical factors were 250 kv., with a half-value layer of 1.6 mm. of copper. An initial tumor dose of 600 r was given. Later, in certain cases, this tumor dose was increased to 800 and 1,200 r. Treatment was not repeated in less than three weeks, and then only if it were actually necessary and if the blood count had returned to normal.

To allay nausea and vomiting, the patients were treated in a fasting state followed by heavy sedation with barbiturates. The toxicity of the combined therapy was that which might be expected from the use of nitrogen mustard or x-rays alone.

Of 26 cases of Hodgkin's disease treated by the combined method, some two-thirds showed significant remissions (up to twenty-six months).

The authors conclude that this combined treatment has its optimum effect in advanced cases of Hodgkin's disease. It is less effective in lymphosarcoma and reticulum-cell sarcoma; a palliative effect is obtained in certain cases of inoperable lung cancer.

Four tables, of which one summarizes the observations in the 52 cases. ROBERT H. LEAMING, M.D.
Memorial Center, N. Y.

A Method to Determine the Shielding Effect in Multiple Radium Sources. R. O. Kornelsen. *J. Canad. Assoc. Radiologists* 3: 67-68, December 1952.

When it is necessary to place a number of radium tubes in one container, the shielding of one tube by another is an important effect, especially when the filtration is heavy. A method of modifying the radium isodose curves to allow for this effect is described. The filtration measured along a single line from the center of one tube is the summation of the thickness of that tube wall and the thicknesses of such portions of the other tubes as lie in the line.

It was found that when tubes of 1 mm. platinum filtration are used in groups of three, four, or five, the added shielding from the contiguous tubes raises the filtration to an average of 1.64, 1.83, and 1.91 mm., respectively.

The method was checked experimentally for the 4-tube arrangement and the figures for the calculated and experimental results were very close. They indicated that the uncorrected figure for radiation delivered would be overestimated by more than 10 per cent if the additional filtration from the contiguous tubes was not considered.

Three drawings. MORTIMER R. CAMIEL, M.D.
Brooklyn, N. Y.

RADIOISOTOPES

Radioiodine in the Diagnosis of Thyroid Disorders. Franz K. Bauer, William E. Goodwin, and Raymond L. Libby. *M. Clin. North America* 36: 981-989, July 1952.

Since I^{131} became available on a large scale for the diagnosis and treatment of thyroid disease, the I^{131} tracer study has become an important diagnostic procedure in clinical medicine and is generally afforded equal importance with the serum protein-bound iodine, the basal metabolic rate, and the serum cholesterol content.

The development of a sensitive gamma-ray detector such as the scintillation counter has made it possible to use doses as small as 1 microcurie of I^{131} for thyroid uptake and urinary excretion studies. This is about 1/100 of the dose that has been commonly used and makes repeated tracer studies possible.

The procedures used in the authors' laboratory are:

1. The I^{131} tracer study with direct measurements of the amount of I^{131} accumulated by the thyroid gland (thyroid uptake).

2. Measurement of the urinary excretion of I^{131} from the same dose which is employed for the thyroid uptake study.

3. Visual delineation of the frontal profile of the thyroid gland.

In healthy controls, the mean thyroid uptake values with their standard deviations were: at six hours, $14.3\% \pm 5.2$; at twenty-four hours, $23.3\% \pm 7.3$.

In hyperthyroidism both the rate of uptake and the total amount of I^{131} collected by the thyroid are increased. The rapid rate of uptake and the increased total amount of I^{131} accumulated by the thyroid gland do not parallel the severity of the disease. In treated hyperthyroidism, whether by surgery, I^{131} , or thiourea derivatives, the initial rapid rate of uptake may persist for years, although the total collected by the thyroid gland is within normal limits.

In hypothyroidism the initial rate of uptake is slow and the total amount of I^{131} accumulated by the thyroid gland is low.

In thyroiditis uptakes are within the normal range or low. In non-toxic goiter uptake values are usually normal or low. In carcinoma of the thyroid, the uptake values are not diagnostic.

The urinary excretion values of I^{131} in healthy controls were found to be: at six hours, $34.7\% \pm 10.2$; at twenty-four hours, $62.7\% \pm 7.9$.

For 23 hyperthyroid patients the corresponding figures were $15.3\% \pm 6.7$ and $18.2\% \pm 9.9$; for 5 hypothyroid patients, $24.4\% \pm 5.3$ and $61.7\% \pm 5.8$.

There are several sources of error or factors which influence the thyroid uptake and urinary excretion of I^{131} . Certain stable iodine compounds, thyroid medication, thiourea derivatives, cortisone, and ACTH will all depress the thyroid uptake of I^{131} .

If a structural change of the thyroid is found to be present or if such a change is suspected, a visualization of the frontal profile of the gland may be obtained. These outlines have been called scintigrams and for this purpose an automatic scanner is used. The amounts of I^{131} employed are between 100 and 250 microcuries, depending on the thyroid uptake. Sixty or seventy microcuries of I^{131} must be present in the thyroid gland in order to obtain a satisfactory scintigram. The indications for this procedure are: (1) hyperthyroidism, (2)

simple goiter, including substernal extension of thyroid glands, (3) solitary nodules, in order to determine whether or not I^{131} is accumulated, (4) carcinoma of the thyroid gland before and after surgical treatment, in order to determine I^{131} pick-up of metastases or remaining thyroid tissue, and (5) suspected aberrant thyroid tissue.

Five scintigrams; 1 photograph; 1 drawing; 2 tables.

BERT H. MALONE, M.D.
Brunswick, Ga.

Evaluation of Treatment of Hyperthyroidism with Radioiodine. Earl R. Miller, Morris E. Dailey, and Horace J. McCorkle. *Arch. Surg.* 65: 12-18, July 1952.

The treatment of hyperthyroidism with radioiodine results from the intraglandular radiation therapy of the abnormal thyroid.

This report is concerned with the first 100 consecutive patients to whom radioiodine was administered for treatment of hyperthyroidism at the University of California Medical School after the present radioiodine laboratory was established in 1945. The patients came from the thyroid clinic of the University of California Medical School and from private physicians. They were accepted for radioiodine treatment under the following conditions: when in the opinion of referring physicians and the physician in charge of the radioiodine laboratory (E. R. M.) they had hyperthyroidism; they were not pregnant; there were no palpable nodules in the thyroid; they were apparently responsible enough to return for follow-up evaluation; they lived near enough to San Francisco so that the follow-up visits were not an undue burden; they were not under the influence of antithyroid medication.

The evaluation of thyroid function before and after treatment was made by the physicians' analyses of the symptoms, signs, and results of the correlative laboratory procedures, such as determinations of the basal metabolism rate, protein-bound iodine, and I^{131} uptake in the thyroid. There is, of course, no method available at present which will determine objectively the correctness of this evaluation. However, recent re-evaluation of the records of these patients indicate that if they were to present themselves they would be accepted for treatment.

The first few patients were treated with small doses of radioactive iodine (250 to 400 μ c of I^{131}) at weekly intervals. No untoward effects or notable successes were observed at this dose level. The dose was increased empirically. When effective apparatus was developed and adequate studies of the physical factors involved in radiation measurements were completed, the initial dose was changed to that amount of radioiodine which would deliver 3,000 beta rep to the thyroid. This radiation dose to the thyroid from the beta particles of I^{131} was calculated from the maximum uptake of radioiodine in the gland, the effective half-life of the I^{131} in the thyroid, and the estimated weight of the thyroid. The initial dose was increased progressively until 6,000 beta rep was adopted as a routine initial dose. Since the first 100 patients were treated, further study of the I^{131} dosage problem has shown that there were considerable discrepancies between the planned treatment dose and the dose of radiation that the thyroid "actually" re-

ceived. Because of these and other studies, the initial treatment dose of I^{131} was changed recently to 120 μ c of I^{131} per estimated gram of thyroid. Subsequent treatment doses, if needed, were 60 or 120 μ c per estimated gram of thyroid, depending upon the clinical condition of the patient.

Of the 91 cases that could be evaluated, remission was achieved in 89, 1 was lost to follow-up, and operation was done in 1 before remission was obtained. In 1 there was definite recurrence, in 6 doubtful recurrences, and in 10 hypothyroidism developed, necessitating treatment with thyroid substance. The follow-up period is from one and one-half to more than five years since the beginning of treatment. No untoward effects have been observed.

Four tables.

BERT H. MALONE, M.D.
Brunswick, Ga.

Blood Levels after Tracer Doses of Radioactive Iodine in the Diagnosis of Thyroid Disorders. Solomon Silver, Mack H. Fieber, and Stephen B. Yohalem. *Am. J. Med.* 13: 725-729, December 1952.

Using a sensitive windowless counter, the authors studied the degree of radioactivity in 1 ml. of whole blood at various periods after intramuscular administration of 100 microcuries of carrier-free I^{131} in 30 controls and 24 hyperthyroid patients. In the euthyroid subject there is a steady fall in radioactivity after the administration of the I^{131} , due to removal of the isotope from the circulation by the thyroid and excretion by the kidneys. In hyperthyroid patients the levels in the blood are at first somewhat less than in euthyroid controls, but at about the eighth hour the curve of radioactivity reverses its direction and begins to ascend, reaching a plateau between forty-eight and ninety-six hours. During this period there was no overlapping of the curves, the lowest values for the hyperthyroid group exceeding the highest for the controls.

Following this study, it became apparent that a single blood specimen obtained at seventy-two hours after administration of the isotope should give diagnostic information if the total radioactivity of 1 ml. of plasma and the radioactivity of the protein fraction were determined. It was also found that the tracer dose could be administered orally. Results are given for a series of 187 euthyroid and 123 hyperthyroid subjects examined by this procedure. As the observations were extended, the absence of overlap between the hyperthyroid and euthyroid subjects was no longer absolute, but only 3 discordant values were obtained in the 310 cases, results better than were achieved with any other test for hyperthyroidism employed.

Two graphs; 2 tables.

The Effects of L-Thyroxine Sodium on Nontoxic Goiter, on Myxedema and on the Thyroid Uptake of Radioactive Iodine. Solomon Papper, Belton A. Burrows, Sidney H. Ingbar, John H. Sisson, and Joseph F. Ross. *New England J. Med.* 247: 897-899, Dec. 4, 1952.

The effects of treatment with l-thyroxine sodium were studied in 23 patients. Thirteen of these had non-toxic goiters and 7 had untreated myxedema. The remaining 3 had been euthyroid while taking thyroid extract and were changed to l-thyroxine. In 7 patients with non-toxic goiter, the uptake of radioactive iodine was determined before and after two to eight weeks of oral administration of l-thyroxine sodium.

Synthetic l-thyroxine suppressed the uptake of radioactive iodine in all patients, reduced the size of the goiter in 7 of the 13 non-toxic cases, and induced remissions in all of the 7 patients with previously untreated myxedema (6 patients became euthyroid in three to eight weeks, and after twelve weeks).

There is apparently no difference in response of patients to l-thyroxine sodium and to thyroid extract. Synthetic thyroxine offers the advantages of uniform strength and composition and greater stability.

Five tables.

RICHARD F. MCCLURE, M.D.
Palos Verdes Estates, Calif.

Scintigrams of the Thyroid Gland. The Diagnosis of Morphologic Abnormalities with I^{131} . Franz K. Bauer, William E. Goodwin, Thomas F. Barrett, Raymond L. Libby, and Benedict Cassen. *California Med.* 77: 380-382, December 1952.

A visual representation of the thyroid gland is made with a directional scintillation counter, after administration of radioactive iodine. A dose of 100-300 microcuries of carrier-free I^{131} is given in a capsule orally. Twenty-four to forty-eight hours thereafter, the scintigram is obtained. The immobilized patient is made comfortable and the scanning tube is run over the neck or other area where functioning thyroid tissue is thought to be present.

This procedure has proved invaluable in the detection and study of both toxic and non-functioning nodules, diffuse enlargement of the thyroid in hyperthyroidism and its reduction in size subsequent to treatment, carcinoma, and aberrant thyroid. Reproductions of scintigrams show the appearances obtained in these various conditions. In an original paper in *RADIOLOGY* (61: 88, 1953), the authors have reported on the use of this procedure in determining the weight of the thyroid.

One roentgenogram; 7 scintigrams.

DONALD DE F. BAUER, M.D.
Coos Bay, Ore.

Use of I^{131} -Labeled Protein in the Diagnosis of Pancreatic Insufficiency. Austin B. Chinn, Paul S. Lavik, Richard M. Stitt, and G. Warren Buckaloo. *New England J. Med.* 247: 877-880, Dec. 4, 1952.

Experiments on dogs have shown that the rise in radioactivity in the blood after ingestion of a meal of I^{131} -labeled protein is distinctly retarded after pancreatectomy. This is in keeping with a diminished hydrolysis of protein in the intestine because of pancreatic insufficiency and should be reflected in pancreatic insufficiency as an increase in the excretion of I^{131} in the feces and a decrease in the urine.

The authors studied the fecal and urinary excretion of I^{131} for a period of seventy-two hours after the administration of a test meal containing I^{131} -labeled protein to 11 patients without gastrointestinal disease and to 5 patients with pancreatic insufficiency. In the control group, the urinary excretion for seventy-two hours ranged from 61.8 to 90.1 per cent of ingested I^{131} , and fecal excretion from 0.5 to 4.8 per cent. In the group with pancreatic insufficiency the urinary excretion for seventy-two hours was significantly lower than in the control group, and fecal excretion was significantly elevated above the normal. When pancreatic extract was administered to the insufficiency group, the urinary excretion of ingested I^{131} rose to a low normal range and the fecal content fell to nearly normal figures. In 2 of

the 5 cases of pancreatic insufficiency, the administration of pancreatic extract failed to cause a significant change in urinary or fecal content from the untreated state.

It is evident that the determination of fecal excretion of isotope can be a useful technic in the evaluation of suspected pancreatic insufficiency. Since urinary values are influenced by factors other than digestion and absorption, excretion of the isotope in the urine does not differentiate between the normal and the insufficient pancreas as clearly as does the fecal measurement. Failure to obtain a more normal absorption of protein following administration of pancreatic extract in 2 patients was possibly due to inadequate hydrolysis of the relatively large quantity of protein included in the test meal (see also Lavik *et al.*: *Pediatrics* 10: 667, 1952. Abst. in *Radiology* 61: 469, 1953).

Two graphs; 2 tables.

RICHARD F. McCLURE, M.D.
Palos Verdes Estates, Calif.

The Intracavitary Administration of Radioactive Colloidal Gold. Raymond G. Rose, Melvin P. Osborne, and William B. Stevens. *New England J. Med.* 247: 663-667, Oct. 30, 1952.

A closed remote system for injecting radioactive gold into the pleural or peritoneal cavity for the treatment of viscid or loculated ascites is described. In contrast to the trocar method, the distribution of the isotope can be made almost uniform with a minimum of posturing. The patient merely changes position at hourly intervals throughout the first waking day and subsequently only as required if distribution is not uniform.

Exposure of administering personnel to radiation is slight, since all are able to remain at a distance from the radioactive material. After injection, the patient becomes a source of radiation. With 100 mc, an activity measuring 50 mr per hour can be noted at the edge of the patient's bed and 5 mr per hour at a distance of 5 feet. Exposure of other patients is a hazard, and such patients must be kept at a distance of at least 6 feet. A nurse may be permitted within 2 feet of the patient for a maximum of twenty minutes per day.

Following injection, the equipment used is rinsed in a continuous flow bath for several hours. It must then be set aside for a period of at least two half-lives before it is monitored and sterilized for re-use.

Three illustrations. DONALD DE F. BAUER, M.D.
Coos Bay, Ore.

The Palliative Treatment of Malignant Pleural and Peritoneal Effusions with Radio-Active Colloidal Gold. R. J. Walton. *J. Fac. Radiologists* 4: 130-133, October 1952.

Many forms of therapy have been tried in patients with pleural and peritoneal effusions secondary to malignant disease. Conventional radiotherapy, along with the other methods, has met with no success, while symptomatic relief from repeated tapping robs the patient of water and needed protein. The author reports his experience with radioactive gold.

Patients in good general condition are benefited more by radioactive gold than those in poor condition. The latter may even suffer a more rapid downhill course and die before therapeutic benefit is obtained.

Of 18 patients treated for pleural effusion, 7 benefited greatly, 4 received some benefit, and 8 showed no re-

sponse. Sixteen patients were given gold for ascites, of whom 5 did well, 5 had some benefit, and 8 failed to respond.

The use of gold at the time of surgery was tried in 10 patients with peritoneal implants. The mean survival was six months, with one patient living two years without evidence of disease.

In 5 patients cysts were ruptured in removal of malignant ovarian masses, and gold was used at surgery. All of this group were living at six months, with evidence of tumor in only 1.

Details of technic and dosimetry are included. The mean dose in the author's cases was 4,000 to 7,000 r.

Two figures; 1 table.

EDWARD E. TENNANT, M.D.
Jacksonville, N. C.

Radioactive Phosphorus Studies in the Diagnosis of Ocular Tumors (A Preliminary Report). Arno E. Town. *West Virginia M. J.* 48: 356-359, December 1952.

The successful use of radioactive tracers in the diagnosis of brain tumors led logically to their trial in ocular tumors, most of which are of nervous or allied tissue. The method consisted of intravenous injection of radioactive phosphorus followed by Geiger counter readings over corresponding areas of both eyes.

Eight cases are reported, including 3 of intraocular tumor. In 2 of these, a melanosisarcoma and a retinoblastoma, the test gave unequivocal results, but in an anaplastic carcinoma the results were not so definite. Four cases were definitely negative (counts over corresponding areas being nearly equal) and in 1 case further studies were to be done, since the increased count which was found might have been due to recent surgery.

The author draws the conclusion that the use of radioactive phosphorus is most helpful in deciding whether a given case of retinal detachment is due to fluid or a tumor.

ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Radioactive Strontium Therapy of the Eye. Corneal Biostandardization and Evaluation of an Applicator for Use in Ophthalmology. Fred M. Wilson and John W. Wilson. *Arch. Ophth.* 48: 686-695, December 1952.

Two radioactive strontium (Sr^{90}) medical applicators (RA-1, Nos. 29 and 153) were evaluated by animal experiments and clinical trial. The minimum inflammatory dose for the rabbit cornea was found to be 35,000 rep for both applicators (these values do not necessarily apply to other, similar applicators). The average clinical dose for the human eye was about 16,000 rep, delivered by single contact.

The advantages of radiostrontium are relative permanency, availability, low-cost beta-ray emission without significant gamma radiation, and beta particles of adequate energy. The disadvantages are prolonged clinical treatment time, a fault which is intensified by the lack of a suitable mechanical holding device; presumably an increased tendency to ulceration and to delayed reactions, as may be inferred from the animal experiments; difficulty of application in certain areas, due to excessive diameter of the instrument, and, at present, unreliability of the physical calibration of applicators as a basis for the calculation of the clinical dose.

Sr^{90} has certain highly desirable features and holds

promise as a source material for use in ophthalmology. Because of the disadvantages of the applicator in its present form, however, it seems advisable to remodel the instrument, especially to improve the design and the dose rate, in order to increase its suitability for beta irradiation of the eye.

One photograph; 5 tables.

Therapeutic Trials of Radiogallium (Ga^{72}). A Report of Four Cases. E. R. King, L. W. Brady, and H. C. Dudley. *Arch. Int. Med.* 90: 785-789, December 1952.

In a preliminary report on the use of Ga^{72} in clinical tracer studies published in *RADIOLOGY* (59: 844, 1952), King and his associates stated that this isotope did not appear too promising as a diagnostic tool. In the 4 cases of bone cancer which they report here a therapeutic trial was equally unpromising. The toxicity of stable gallium limits the amount of radioactive gallium that can be administered and thus eliminates its use as a therapeutic agent under present methods of preparation and administration.

[An extended report on radiogallium by Brucer and his associates appears in this issue of *RADIOLOGY* (pp. 534-613).]

One table.

Comparison of the Thiocyanate and Radiosodium Spaces in Disease States. Jerry K. Aikawa, with the technical assistance of Eloise Rhoades. *Am. J. M. Sc.* 224: 632-637, December 1952.

Until recently the thiocyanate method was the only

practical one available for the estimation of the extracellular fluid space in clinical studies. In normal individuals the thiocyanate space is practically identical with the radiosodium space. The author here attempts to compare the volumes of fluid available for dilution of the thiocyanate and radiosodium ions in various diseases.

The studies were carried out on 25 hospitalized patients and 4 normal subjects used as controls. In the normal subjects the volumes of fluid available for dilution of these ions were practically identical. Of the 39 determinations in persons with disease states, 18 showed the radiosodium space to be greater than the thiocyanate space and in 21 instances the reverse was true. No pitting edema was found in patients with a Na_{24} volume of less than 330 ml./kg. When the Na_{24} space exceeds this figure, it can no longer be correlated with total blood volume; below this level there is a rough correlation—the higher the radiosodium space, the larger the total blood volume.

The author discusses interstitial edema formation due to decreased renal excretion, the state of the intercellular cement system, and the integrity of the tissue cell membrane as factors influencing the radiosodium and thiocyanate spaces. He notes that both thiocyanate and radiosodium space determinations measure a volume of fluid which is greater than the usually accepted extracellular fluid space but suggests that the radiosodium method is a measurement of physiologic significance.

Two figures; 1 table showing the fluid volume data for the subjects examined.

BERTRAM LEVIN, M.D.
Minneapolis, Minn.

RADIATION EFFECTS

Further Efforts to Influence X-Ray Cataract by Chemical Agents. Ludwig von Sallmann, with the technical assistance of Carmen M. Munoz. *Arch. Ophth.* 48: 276-291, September 1952.

In 1951, the author and his co-workers (*Am. J. Ophth.* 34: 95, 1951) reported on the relation of treatment with cysteine to the x-ray damage of rabbit eyes which had been exposed to a single dose of 1,500 r of penetrating x-rays. It was concluded that the usual signs of radiation damage in the region of the eye, such as keratoconjunctivitis, transient iritic changes, and pigment proliferation from the limbus into the cornea, were not influenced greatly by pretreatment of the animals with this amino acid. On the other hand, complete epilation of the exposed lids, which regularly takes place as a result of this dose of x-rays, was prevented by intravenous injection of cysteine (2 gm. per animal) prior to the irradiation. It was shown, moreover, that the onset of radiation cataract could at least be greatly delayed if the radiation was not administered to the eyes until five to thirty minutes had elapsed after the use of the chemical compound.

The present study was divided into three parts. First, it had to be shown by prolonged observations whether the reported early beneficial effect of cysteine treatment on x-ray damage of the lens was of transient or relatively permanent character, and whether it could be influenced by additional use of the amino acid at later periods. Second, the development of microscopic signs of x-ray damage was analyzed in the eyes irradi-

ated before and after the intravenous use of cysteine. Finally, investigations were carried out on the influence of thiols other than cysteine, of compounds classified as reductants or antioxidants which did not contain —SH groups, of a substance known as citrovorum factor, which supposedly protects certain phases of mitotic activity, and of a metabolic poison.

It was found that intravenously administered cysteine had a strong protective action against radiation damage to the lens and hair follicles of rabbits when the treatment preceded the exposure of the eye to 1,500 r. This protective influence had persisted to the time of the report, at least eighteen months. When cysteine was injected subconjunctivally twice weekly for three weeks after the irradiation of cysteine-pretreated rabbits, the fine cortical opacities were not reduced by the additional therapy. Subconjunctival injection of 1.0 c.c. of an 8 per cent solution of cysteine prior to irradiation was moderately beneficial in preventing the damage to the lens by local exposure of the eye to 1,500 r.

Analysis of microscopically visible changes in the lens, which develop in the first two or three weeks after irradiation with 1,500 r, showed that almost all lesions were less pronounced in the cysteine-pretreated eyes than in the eyes irradiated before the use of cysteine.

X-ray-induced inhibition of cell division, recovery, and compensatory increase of mitotic activity of the lens epithelium differed very little in cysteine-pretreated animals and in non-pretreated controls.

Under the conditions of the experiment, glutathione and thiourea were less effective than cysteine in increasing the radioresistance of sensitive elements of the lens. Sodium thioglycollate and dimercaprol (BAL) were totally ineffective. Pretreatment with other reducing chemical agents (dihydroxyacetone and tocopherol), with the citrovorum factor, and with cyanide did not reduce the injurious effect of 1,500 r applied locally to the rabbit eye.

Two figures; 4 tables.

Radiation Exposure in the United States. Dade W. Moeller, James G. Terrill, Jr., and Samuel C. Ingraham, II. Pub. Health Rep. 68: 57-65, January 1953.

The human race has always been exposed to some ionizing radiation from cosmic rays and other natural sources. It is estimated that during a lifetime of seventy years this exposure amounts to about 9 r. Today, however, this constitutes only a small portion of the radiation received by the average individual. The authors devote their attention here to other sources of radiation, without considering control of exposure or public health effects of the radiation received.

More than 125,000 x-ray units are being used for diagnosis and therapy in the United States, and over 215,000 medical-technical personnel are potentially exposed to radiation in the operation of these units. A survey of personnel discloses that 3 per cent receive more than the maximum permissible dose of 0.3 r per week. Operators of dental x-ray machines receive approximately 0.1 r of general body radiation per eight mouth examinations. In addition to the operators, a considerable number of the 2,500,000 persons seen daily by physicians are exposed to radiations. Twenty-five million radiographic examinations are carried out annually by radiologists, and the authors estimate that the average exposure is 11 r per examination. In addition, 4,000,000 x-ray treatments are given annually by radiologists. Probably the largest single source of medical radiation exposure in the United States is the mass x-ray survey for tuberculosis. In 1950, approximately 15,000,000 persons were examined, with an estimated exposure of 1.0 r per examination.

There are approximately 2,000 industrial fluoroscopic and radiographic units in operation today, with about 5,000 persons involved in their operation. Most of the permanent installations have been well planned for protection of the operator. Fluoroscopy is used at times for scanning personnel to detect pilfering, with a resultant exposure of 0.045 to 0.09 r per "subject" for each inspection.

Fluoroscopy in shoe-fitting results in a dose of 7 to 14 r to the customer's feet and 0.03 to 0.17 r to the pelvis, per twenty-second exposure. Ten thousand of these fluoroscopes are in operation, with potential exposure of 30,000 to 40,000 sales people.

The authors discuss, also, the exposures that are encountered in research with high-voltage equipment. Fifteen hundred x-ray diffraction units are in operation and scattered radiation of intensities up to 1.0 r per hour have been recorded. The 500 electron microscopes in use also may give off scattered radiation up to 1.5 r per hour.

Radioactive isotopes are being used by 900 universities, hospitals, and research laboratories, and it is estimated that 7,500 persons are involved in the use of these materials. Cobalt 60 is being used at present in about 80 industries in the United States. Within the next few years, it is anticipated that the industrial uses of fission products will become widespread.

Many individuals are potentially exposed to radiation in the medical use of radium. Radium exposure is also possible in industrial radiographic installations, and in use of the element as a self-luminous paint. Static eliminators containing radioactive material are also widely used in some industries (textile, paper, photographic processing, telephone and telegraph).

Other sources of radiation discussed by the authors include the operation of nuclear reactors and the 100 particle accelerator units (cyclotrons, synchrotrons, etc.) now in operation. Many of the activities sponsored by the Atomic Energy Commission may result in radiation exposure. These include uranium mining and milling, nuclear reactor operations, and testing of weapons.

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Baton Rouge, La.



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